Additive effects of aging and HIV infection on category verbal fluency: an analysis of component processes

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Additive Effects of Aging and HIV Infection on Category Verbal Fluency: An Analysis of Component Processes

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in

Clinical Psychology

by

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2011
The Dissertation of Jennifer E. Iudicello is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego
San Diego State University
2011
DEDICATION

To all of my family and friends

who have supported me through the years

xoxo
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CLINICAL EXPERIENCES

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**Honors and Awards**

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ABSTRACT OF THE DISSERTATION

Additive Effects of Aging and HIV Infection on Category Verbal Fluency: An Analysis of Component Processes

by

Jennifer E. Iudicello

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2011
San Diego State University, 2011

Professor Steven Paul Woods, Chair

Advances in the management of HIV infection have resulted in a growing population of older adults living with HIV. Both aging and HIV infection have been independently associated with central nervous system changes and corresponding declines in neurocognitive functioning. Poorer semantic verbal fluency output is also
common in both HIV infection and healthy older adults, although, the possible additive effects of these risk factors are unknown. The present study aimed to examine the combined effects of aging and HIV on semantic verbal fluency and its component processes (i.e., clustering and switching), the neurocognitive correlates of clustering and switching in older HIV-infected adults, and the associations between clustering and switching and everyday functioning.

Participants included 257 individuals across 4 demographically matched groups: Younger (i.e., <40 years) Healthy (n=93), Younger HIV-infected (n=50), Older (i.e., ≥50 years) Healthy (n=51), and Older HIV-infected (n=63) individuals. Participants were administered a standard semantic fluency protocol scored according to established clustering and switching guidelines (Troyer et al., 1997) and a self-reported assessment of everyday functioning as part of a comprehensive neuropsychological, medical, and psychological evaluation. Jonckheere-Terpstra tests revealed a significant stepwise additive effect between the groups for overall semantic fluency output (p = 0.004) and a trend for declining switching performance (p = 0.056), but not cluster size (p = 0.826), with greatest deficits evident in the Older HIV-infected participants. Results were not better explained by confounding psychiatric, medical, or HIV disease characteristics. Within the older HIV-infected adults, poorer switching was associated with deficits in learning and executive functioning and self-reported declines in everyday functioning. Results suggest that HIV infection and aging may confer adverse additive effects on the executive components of semantic fluency (i.e., switching), which was associated with poorer everyday functioning outcomes and may be driven by the combined frontostriatal neuropathological burden
of these two conditions. This research provides preliminary insight into the cognitive architecture of HIV-associated neurocognitive disorders among older adults, and may ultimately guide rehabilitation efforts aimed at improving overall quality of life for the growing population of older adults living with HIV infection.
I. Introduction

Aging and HIV infection

With advances in the treatment of HIV infection, the incidence and prevalence of older individuals living with HIV/AIDS has steadily increased over the past 10 years. The Center for Disease Control and Prevention estimated that 135,000 individuals over the age of 50 were living with AIDS in the United States in 2006, which nearly doubles the 2002 estimates. Moreover, the number of older (i.e., over 50 years of age) individuals with AIDS represents over 30% of the total estimated number of persons currently living with AIDS in the United States (Centers for Disease Control and Prevention, 2007). Despite the growing number of older individuals living with HIV/AIDS, much of the extant literature on the neurocognitive deficits in HIV infection has focused on younger and middle-aged adults. However, both HIV infection and aging have been established as independent risk factors for cognitive impairment. Moreover, both HIV-associated and age-related neurocognitive decline are associated with functional consequences, including self-reported difficulties with instrumental activities of daily living (IADLs; Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000; Heaton et al., 2004). Thus, there is a clear need for research investigating the nature and extent of age-related cognitive decline in older individuals with HIV infection. Such research may provide insight into the neuropsychological profile of HIV-infected older adults, which will be essential in the development of more effective strategies that may be used for cognitive rehabilitation purposes and improvements in overall quality of life.
Below I will first review the independent effects of HIV infection and aging on the central nervous system (CNS), followed by a discussion of the existing literature of the concomitant effects of HIV infection and aging on cognition. I will then provide a general discussion of verbal fluency, including a summary of existing research on category verbal fluency performance (as category verbal fluency will be my primary focus) and category fluency component process analyses (i.e., clustering and switching) in HIV infection and aging populations. After presenting the background research, I will state the aims and hypothesis of this dissertation, present the methods and analyses that were used to explore the stated hypotheses, followed by the results, conclusions, limitations, future directions, and clinical implications.

**NeuroAIDS**

HIV invades the central nervous system (CNS) early in the course of infection and leads to widespread immunological and neurological damage (Gonzalez-Scarano & Martin-Garcia, 2005). Although unable to cross the blood brain barrier (BBB) independently, HIV is thought to enter the CNS (Wu et al., 2000) by infecting monocytes and cluster of differentiation 4+ (CD4+) lymphocytes (Haase, 1986) migrating across the BBB. This infiltration leads to neuropathological damage through both direct (e.g., viral) and indirect (e.g., astrocytosis) mechanisms. While both monocytes and CD4+ cells are thought to facilitate the transport of HIV infection across the BBB, the relationship between CD4+ T cells and viral replication once across the BBB remains unclear. However, similarities between HIV found in the brain relative to that found in HIV-infected monocytes suggests an active role of these
cells in the production and replication of the virus. Specifically, once across the BBB, HIV-infected monocytes may differentiate into perivascular macrophages and/or infect microglia, leading to the replication and production of the virus and HIV-associated brain injury, in part due to the release of neurotoxic substances (e.g., viral envelope proteins, cytokines, and chemokines; Kaul, Garden, & Lipton, 2001). In addition to their independent associations with HIV viral replication, the infected microglia and macrophages may fuse together to form multinucleated giant cells, which were historically considered to be a hallmark feature of HIV neuropathology, and have been found in the hemispheric white matter and basal ganglia (Bell, 2004; Budka et al., 1987). Activation of the microglial system is not specific to HIV infection, but is also involved in co-morbid conditions associated with HIV infection, including neurodegenerative disorders (e.g. Alzheimer’s disease; Williams & Hickey, 2002).

While macrophages and microglia are the most common cell types vulnerable to HIV infection, it has also been suggested that astrocytes may also be involved in HIV-associated neuronal damage, albeit indirectly. Specifically, neurotoxic molecules released by activated microglia and macrophages (e.g., gp120) can activate astrocytes, leading to an increase in brain chemical (e.g., glutamate) concentrations and neurotoxins that may subsequently result in neuronal injury (e.g., Genis et al., 1992). The inflammatory cascade instigated by astrocytes, microglia and macrophages may lead to HIV encephalitis (HIVE), which includes features such as microgliosis, myelin pallor, and the presence of multinucleated giant cells, and has been linked to HIV-associated dementia (HAD; e.g., Wiley, Masliah, & Achim, 1994). Thus, while HIV
does not directly infect neurons (Takahashi et al., 2004), the activation of astrocytes, microglia, and macrophages may result in widespread glial and neuronal pathologies, which are evident in approximately 50% of HIV infected individuals with dementia (Glass, Wesselingh, Selnes, & McArthur, 1993; Navia, Jordan, & Price, 1986).

Structural (e.g., atrophy, white matter hyperintensities) and functional (e.g., abnormal brain perfusion) brain abnormalities in HIV-infected individuals have been well documented, and are commonly found in areas including the striatum (i.e., caudate nucleus and putamen), frontal cortex, hippocampus, and cerebral white matter (e.g., Aylward et al., 1995; Chang, Ernst, Leonido-Yee, & Speck, 2000; Chang, Ernst, Speck, & Grob, 2005; Everall, Barnes, Spargo, & Lantos, 1995; Jernigan et al., 1993; Oster et al., 1993; Moore et al., 2006; Tran Dinh, Mamo, Cervoni, Caulin, & Saimot, 1990). HIV-associated neural changes have been demonstrated throughout the course of HIV infection, with and without cognitive disturbance, and tend to become more prevalent and severe with HIV disease progression (Jernigan et al., 1993; Stout et al., 1998; Taylor et al., 2007). For example, white matter abnormalities, one of the most frequent neuropathological features of HIV infection, have been demonstrated throughout the brain (e.g., frontal and subcortical white matter, corpus collosom; Filippi, Ulu, Ryan, Ferrando & van Gorp, 2001; Pomara, Crandall, Choi, Johnson, & Lim, 2001), and even in the medically asymptomatic stage of disease (e.g., Wilkinson et al., 1997). Moreover, white matter abnormalities have been linked to HIV-associated cognitive impairment (e.g., Aylward et al., 1995; Gongvatana et al., 2009; Hall et al., 1996), may be more prevalent and severe in individuals with advanced disease (Gray et al., 1997; Jernigan et al., 1993), and have been associated with post
Numerous studies have also shown that the basal ganglia and frontostriatal circuits may be particularly vulnerable to HIV infection (e.g., Aylward, et. al., 1993; Everall et al., 1995; Itoh, Mehraein, & Weis, 2000; Reyes, Faraldi, Senseng, Flowers, & Fariello, 1991). For example, prominent atrophy has been observed throughout the course of HIV infection in the basal ganglia (Oster et al., 1993; Stout et al., 1998), with the most pronounced volume loss found in those with HIV-associated dementia (e.g., Aylward et al., 1993). In addition, frontal brain region abnormalities (e.g., neocortical thinning) are evident in HIV infected individuals with AIDS, and have been strongly associated with cognitive decline (e.g., presence of dementia; Thompson et al., 2005). Moreover, research has demonstrated prominent neuropathological changes in the mediotemporal regions in individuals with HIV associated dementia complex (ADC; e.g., Brew, 2004; Wiley et al., 1998). This evidence of regional vulnerability to HIV is consistent with research demonstrating higher HIV viral loads in the striatum and prefrontostriatal white matter connections (e.g., Masliah et al., 1997), and with evidence from autopsy studies demonstrating greater postmortem neural degeneration in the striatum and hippocampus (Anthony, Ramage, Carnie, Simmonds, & Bell, 2005). Moreover, the extent of synaptodendritic injury to these regions has been correlated with neuropsychological impairment (Brew, 2004; Everall et al., 1999; Masliah et al., 1997; Moore et al., 2006).

The introduction of combination antiretroviral therapies (cART) in 1996 dramatically influenced the clinical course of HIV infection, leading to a number of improvements in HIV disease outcomes. Specifically, effective cART use has been
associated with reduced HIV viral loads and partial restoration of immune function, leading to a decrease in the frequency of CNS opportunistic infections (Centers for Disease Control and Prevention, 2009), reduced mortality rates (Everall et al., 2009; Price & Sprudich, 2008), and an improvement in overall quality of life (Powderly, 2002). cART has also led to changes in the neuropathology of HIV infection. For example, while some aspects of brain pathology (e.g., markers of HIV; Ellis, Calero, & Stockin, 2009) have become less prevalent with advances in treatment, other HIV associated structural and functional brain changes (e.g., synaptodendritic injury, inflammatory white matter changes) still persist, possibly in part due to chronic inflammation, viral replication, or co-morbid factors (e.g., Hepatitis C co-infection, aging).

The epidemiology of HIV-associated neurological disease has also changed since the advent of cART. For instance, data from the Multicenter AIDS Cohort Study (MACS) suggested that shortly after the introduction of cART, the incident rates of HIV-associated dementia (HAD) decreased by nearly 50% relative to rates prior to the cART era (e.g., early 1990s; Sacktor et al., 2001). In recent years, prevalence estimates of HAD in HIV-infected individuals have ranged from 5-15% (Tozzi et al., 2005). Importantly, prevalence rates of HAD appear to be decreasing even further, as current data from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study revealed prevalence rates of only 2% (Heaton et al., 2009). Nevertheless, the prevalence of more mild forms of HIV-associated neurocognitive disorders (HAND) continues to be a problem, despite the systemic effectiveness of antiretroviral
treatment (Ances & Ellis, 2007; Grant, 2008), and can significantly interfere with an individual's ability to carry out everyday activities (e.g., Heaton et al., 1995).

Recent prevalence rates of neuropsychological impairment in HIV infected individuals suggest that cognitive deficits are found in approximately 52% of individuals with HIV infection (Heaton et al., 2009), and are thought to reflect widespread synaptodendritic injury, particularly involving fronto-striato-thalamo-cortical circuits. As these cognitive symptoms vary in prevalence and severity amongst HIV-infected individuals, classification systems have been developed and modified over the years in order to assist in the identification of HAND and to formulate more accurate diagnoses and effective treatments.

The most recent criteria (Antinori et al., 2007) have identified three possible research diagnoses for HAND: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND) and HAD. Among HIV-infected individuals with cognitive deficits, approximately 33% are classified as ANI (Heaton et al., 2009), meaning that they demonstrate HIV-associated (i.e., not due to other factors) cognitive impairment (i.e., ≥1 standard deviation below the normative mean) in two or more cognitive domains, without any disturbance in everyday functioning. About 12% of neuropsychologically impaired HIV infected individuals are classified as having MND (Heaton et al., 2009), which is similar to ANI, although this diagnosis requires an impairment in everyday functioning. Finally, as mentioned above, approximately 2% of those impaired suffer from HAD (Heaton et al., 2009). A diagnosis of HAD requires acquired moderate to severe cognitive impairment (i.e., at least 2 standard deviations below normative means) in at least two cognitive domains,
as well as marked difficulty in everyday functioning due to the cognitive impairment.

For each of these diagnoses, the cognitive impairment (and functional declines) must not be better explained by co-morbid conditions or delirium.

Consistent with a primarily frontostriatal pathophysiology, HIV associated cognitive deficits can be present even in the asymptomatic phase of infection (e.g., Heaton et al., 1995), and have been commonly observed in the areas of learning and memory, attention and working memory, information processing speed, motor skills, and executive functions (Reger, Welsh, Razen, Martin & Boone, 2002). In contrast, basic language abilities, semantic memory, and visuospatial abilities are typically less affected (e.g., Cysique, Maruff, & Brew, 2006). In general, while the presence and magnitude of HIV-associated cognitive deficits vary across individuals, at a group level, HIV-associated cognitive impairments, particularly executive dysfunction, slowed information processing, and motor deficits, become more pronounced as the disease progresses (Reger et al., 2002), and may improve with targeted antiretroviral therapy (Letendre et al., 2004).

Of important clinical relevance, approximately 50% of HIV-infected individuals with cognitive impairment experience problems with daily functioning. Specifically, HIV-associated cognitive impairment has been demonstrated as an independent predictor of dependence in IADLs (e.g., cooking, financial management, medication management; Heaton et al., 2004), and has been associated with poorer vocational functioning (van Gorp, Baerwald, Ferrando, McElhiney & Rabkin, 1999), automobile driving (Marcotte et al., 2004), and medication adherence (Hinkin et al., 2002; Woods et al., 2008). For example, HIV-associated global cognitive impairment
was associated with a two-fold greater risk of poorer medication adherence, independent of co-morbid risk factors including a history of psychiatric (e.g., bipolar disorder) or neurologic (e.g., opportunistic infection) disorders (Hinkin et al., 2002). In addition, HIV-associated prospective memory deficits, which may be characterized primarily by executive dysfunction and impairment in episodic memory, have been significantly associated with poorer self-reported medication management, even after considering effects of demographics, disease severity, and affective distress (Woods et al., 2009a). Research has also found a significant association between HIV-associated cognitive deficits, particularly in the areas of fine motor coordination, episodic memory, executive functioning, and information processing speed, and reduced health related quality of life in HIV-infected individuals (Tozzi et al., 1993). Finally, HIV-associated cognitive impairment has been demonstrated as an independent risk factor for mortality in HIV infection (Ellis et al., 1997), even when considering disease progression, treatment effects, and demographic factors (Sevigny et al., 2007).

One possible explanation for the variability of cognitive impairment found in HIV infected individuals is the number of co-morbid conditions (e.g., medical, psychiatric, and substance use disorders) that are highly prevalent in HIV-infected individuals, and have been well established as independent risk factors for cognitive impairment. Thus, a large body of research has addressed the potential interactive effects of HIV infection and common co-morbidities on neurocognitive functioning, in hopes of clarifying the etiology of the cognitive deficits found in HIV infected individuals. Below I will review the independent effects of a few of the more prevalent co-morbidities in HIV-infected individuals (i.e., depression, alcohol use, illicit
substance use, and hepatitis C virus) on the CNS, as well as the potential interactive
effects of these co-morbidities with HIV infection on brain structure and function.

**Depression and HIV infection.** Major depressive disorder (MDD) is common
in HIV infection, with prevalence rates reaching as high as 50% (Ciesla & Roberts,
2001). MDD may share similar pathological features (e.g., frontostriatal circuits) to
HIV infection (e.g., Tekin & Cummings, 2002), and has been independently
associated with subtle cognitive decline in areas including attention, psychomotor
speed, learning and memory, and executive functioning (e.g., Austin et al., 1992;
Cassens, Wolfe, & Zola, 1990). Despite the similar underlying neural abnormalities
associated with both HIV infection and MDD, most studies have failed to find additive
or synergistic effects of depression and HIV infection on cognition (e.g., Cysique et
al., 2007; Grant et al., 1993; Rourke, Malman, & Bassel, 1999). However, of clinical
importance, research has demonstrated that in HIV-infected individuals, depression is
a strong predictor of dependence in IADLs (Heaton et al., 2004), mortality (Ellis et al.,
1997), and has been associated with poorer health related quality of life (Trepanier et
al., 2005).

**Alcohol use and HIV infection.** Alcohol use disorders are also common in
HIV infection. A national probability sample reported that approximately 8% of HIV-Infected individuals report heavy alcohol use (Galvan, Bing, & Fleishman, 2002),
which is nearly double that of the general population (i.e., 4.5%; Greenfield, Midanik,
& Rogers, 2000). Neuroimaging studies have revealed that HIV infected individuals
with a history of alcohol use demonstrate greater ventricular volume and white matter
hyperintensities (e.g., Pfefferbaum et al., 2006), metabolite alterations (e.g., reductions
in n-acetyl aspartate; Pfefferbaum, Adalsteinsson, & Sullivan, 2005), as well as abnormalities within the structural integrity of the white matter (e.g., lower fractional anisotropy in the corpus collosum; Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007) and subcortical grey matter (e.g., Meyerhoff, Cardenas, & Weiner, 2001), when compared to HIV-infected individuals without histories of alcoholism. A number of studies have also demonstrated evidence of adverse additive and/or synergistic effects of HIV and alcohol use on cognitive functioning, particularly in areas including psychomotor and visuomotor speed (e.g., Green, Saveanu, & Bornstein, 2004; Rothlind et al., 2005), verbal reasoning and auditory processing (e.g., Green et al., 2004), attention (e.g., Schulte, Mueller-Oehring, Rosenbloom, Pfefferbaum & Sullivan, 2005), and reaction time (e.g., Green et al., 2004). Alcohol use has also been shown to accelerate the progression of HIV disease (e.g., Wang et al., 2002), reduce the effectiveness of cART (e.g., Braithwaite et al., 2005), and reduce the health related quality of life (e.g., Rosenbloom et al., 2007) in HIV infected individuals.

**Substance use and HIV infection.** A number of studies have found evidence of both independent effects of substance use, as well as combined effects of substance use and HIV infection on the CNS (e.g., Grassi et al., 1995, Rippeth et al., 2004). For example, methamphetamine (MA) is one of the most common drugs of abuse in HIV infection, and may target brain regions similar to those vulnerable to HIV-associated damage (e.g., basal ganglia, frontal gray and white matter; Chang, Alicata, Ernst & Volkow, 2007; Chang et al., 2005; Sekine et al., 2001; Volkow et al., 2001). MA use has been independently associated with cognitive decline, with a recent meta-analysis
demonstrating moderate deficits in the domains of episodic memory, executive functions, information processing speed, motor skills, language, and visuoconstruction (Scott et al., 2007), possibly reflective of similar frontostriatal neurotoxicity to that seen in HIV infection. Given these similar underlying brain regions that may be vulnerable to both HIV infection and MA use, it is not surprising that research on the combined effects of HIV and MA have demonstrated additive effects on brain structure and function (Carey et al., 2006; Chang et al., 2005; Nath et al., 2002; Rippeth et al., 2004; Taylor et al., 2007). For example, imaging research has demonstrated profound additive neuronal loss or dysfunction in the frontal gray and white matter, as well as in the basal ganglia, in MA-dependent HIV infected individuals, which exceeded the damage observed in participants with only one risk factor (i.e., MA-use or HIV-infection), and in non-MA using seronegative controls (Chang et al., 2005). In addition, Rippeth et al., (2004) found greater rates of cognitive impairment in HIV-infected individuals with a history of MA use relative to non-MA using HIV-infected individuals, HIV seronegative MA-users and HIV seronegative individuals without a history of MA use. Moreover, cognitive impairments may be more pronounced in HIV-infected MA users with more advanced HIV disease (Carey et al., 2006).

**Hepatitis C Virus (HCV) and HIV co-infection.** The hepatitis C virus (HCV) is also common in HIV-infected individuals and has been identified as a risk factor for cognitive impairment both independently and within HIV-infected adults (e.g., Tozzi et al., 2005). Recent prevalence estimates of HIV/HCV co-infection suggest that approximately 20-30% of HIV infected individuals are also co-infected with HCV.
virus, with prevalence rates ranging from 50-90% in HIV infected injection drug users (Centers for Disease Control and Prevention, 2009). Research has demonstrated significant neural injury (e.g., cerebral metabolite abnormalities) resulting from HCV infection alone, in areas including the basal ganglia and frontal white matter (e.g., Forton et al., 2001; Forton et al., 2008). In addition, approximately one third of HCV monoinfected individuals also demonstrate cognitive impairment (Fontana et al., 2005) consistent with a frontostriatal neuropathogenesis similar to HIV, and commonly found in areas of attention, information processing speed, and verbal memory (Perry, Hilsabeck, & Hassanein, 2008; Hilsabeck, Perry, & Hassanein, 2002; Hilsabeck, Hassanein, Carlson, Ziegler, & Perry, 2003).

While the effects of HIV and HCV co-infection on the CNS are less well determined, a large number of studies that have examined the potential interactions between HCV and HIV have found evidence of greater cognitive impairment in HIV/HCV co-infected individuals (e.g., Martin et al., 2004; Hilsabeck, Castellon, & Hinkin, 2005; cf. Perry et al., 2005), relative to individuals with either HIV and HCV infection alone. In addition, recent evidence has found a possible association between the mild cognitive impairment found in HIV/HCV co-infected individuals and abnormal cerebral metabolism (e.g., elevated mI/creatine) in the frontal white matter (Forton et al., 2008). Of clinical importance, HCV and HIV co-morbidity has been associated with poorer self-rated health related quality of life related to individuals with HIV infection alone (Baum et al., 2008).
The Aging Brain

Age is another potentially important co-factor in the expression of HAND. Life expectancy has increased over the last century, resulting in a growing elderly population, and a greater clinical and research interest in the effects of normal aging on brain functioning and behavior. Structural (e.g., volume loss; Drachman, 2006, Burke & Barnes, 2006) and functional (e.g., decreased hemodynamic response; D’Esposito, Zarahn, Aguirre, & Rypma, 1999) brain changes associated with normal aging have been well established in the literature. Specifically, structural effects of aging (e.g., atrophy, increased white matter abnormalities) appear to be most prominent throughout the prefrontal cortex and striatum (Drachman, 2006; Jernigan et al., 1991), with effects also commonly found in the temporal lobes, cerebellum, and deep white matter (Jernigan et al., 2001; Raz & Rodrigue, 2006). White matter abnormalities (e.g., white matter hyperintensities) are apparent in approximately 50% of older individuals even without associated clinical symptoms (Meyer, Kawamura, & Terayama, 1992). Moreover, aging has been associated with reduced synaptodendritic complexity, which may ultimately disrupt brain circuits mediating higher-level cognitive processes (Dickstein et al., 2007).

Cognitive changes are also associated with aging and may be mediated by the above-described age-related changes in brain structure (e.g., volume loss in the prefrontal cortex and loss of frontal white matter integrity; West, 1996). While variable in terms of severity amongst individuals, older adults demonstrate a greater incidence (e.g., Park et al., 2003) and prevalence (e.g., Verhaegen & Salthouse, 1997) of cognitive impairment relative to their younger counterparts. Cognitive declines
associated with aging are most often observed in executive functioning, episodic memory, working memory, and information processing speed (Wilson, Bennett, & Swartzendruber, 1997), the latter of which has been posited to underlie much of the cognitive decline associated with age (Salthouse, 1996). Of clinical significance, the adverse effects of aging on cognition may interfere with everyday functioning (Verhaeghen & Salthouse, 1997), and have been associated with declines in IADLs even while considering potentially confounding effects of depression, other demographics, and general health status (Cahn-Weiner, et al., 2000). In addition, nondemented older adults who show evidence of cognitive decline may be at greater risk for dementia (e.g., Twamley, Ropacki & Bondi, 2006) and mortality (e.g., Schupf et al., 2005).

One particular challenge when examining cognitive change in older adults is the number of co-morbid conditions (e.g., medical, psychiatric, and substance use disorders) common in the elderly that may accelerate the effects of normal aging on the brain and/or may pose additional risk for cognitive impairment in older individuals. Below I will briefly review some of the more prevalent co-morbid conditions in the elderly and discuss the potential adverse effects that they may impose on brain structure and function in older individuals.

**Cerebro- and cardiovascular disease and aging.** Risk factors for cerebro-and cardiovascular disease are commonly found in elderly individuals. Research has shown prevalence rates of hypertension and hypercholesterolemia among older (i.e., over 55 years of age) adults to be approximately 65% and 18%, respectively, with prevalence rates of diabetes among individuals over the age of 60 reaching close to
23% (National Center for Health Statistics, 2009). Studies have found associations between vascular risk factors such as hypertension and diabetes and neural abnormalities (e.g., cortical and subcortical atrophy and white matter hyperintensities; Carmelli et al., 1999; Harrington, Saxby, McKeith, Wesnes, & Ford, 2000; Manschot et al., 2006; van Harten et al., 2007) that appear to closely resemble those found in normal aging. In addition, both hypertension (e.g., Harrington, et al., 2000) and diabetes (e.g., Manschot et al., 2006; van Harten et al., 2007) have been associated with cognitive deficits, specifically in cognitive domains including executive functions, speed of information processing, attention, and memory. While fewer studies have found significant associations between high cholesterol levels and declines in specific cognitive domains, there is evidence that higher midlife cholesterol rates may be associated with an increased rate of dementia (e.g., Anstey, Lipniki, & Low, 2008).

**Neurodegenerative disorders and aging.** Neural changes and corresponding cognitive impairment consistent with neurodegenerative processes (e.g., Alzheimer’s disease, Vascular Dementia) may also overlap with the changes that are commonly observed in the elderly. For example, Alzheimer’s disease is the most common cause of dementia, accounting for approximately 50% of cases (Kawas & Katzman, 1999), and can lead to diffuse neuropathological and neuropsychological changes. While spatial patterns of brain atrophy can generally distinguish normal aging from Alzheimer’s disease, research has demonstrated that the neural pathology (e.g., neuronal atrophy, neurofibrillary tangles and amyloid plaques) associated with Alzheimer’s disease may be evident prior to the presentation of clinical symptoms,
and may mimic that which is seen in clinically normal elderly individuals (e.g., Knopman et al., 2003), albeit not always of similar severity. In addition, although research has identified patterns of neuropsychological impairment that has helped distinguish the cognitive impairments evident during the earlier stages of Alzheimer's disease from the cognitive decline observed in the normal aging process (e.g., Butters et al., 1988), both normal aging and Alzheimer's disease have been associated with declines in several domains including learning and memory, executive functions, and information processing speed (Salmon & Bondi, 1999).

**Psychiatric disorders and aging.** Psychiatric disorders (e.g., depression) frequently occur in the elderly and have been established as risk factors for cognitive impairment. According to the National Center for Health Statistics (2009), depression symptoms are found in approximately 6% of elderly individuals. Imaging studies have revealed evidence of neural abnormalities in depressed elderly individuals, including white matter hyperintensities (Lesser et al., 1996; Taylor et al., 2003) and volume reductions in the hippocampus and both frontal and subcortical (e.g., caudate nucleus) regions (Ballmaier et al., 2004; Bell-McGinty et al., 2002). In addition, depression may also be associated with cognitive dysfunction in older adults (i.e., over age 50), with studies demonstrating cognitive declines in domains including attention, memory, executive functioning, and information processing speed (Butters et al., 2004; Lesser et al., 1996; Rapp, et al., 2005).

**Alcohol use and aging.** Prevalence rates of heavy alcohol use are approximately 2-8% for individuals over 50 years old (Substance Abuse and Mental Health Services Administration, 2009). While controversy exists with regard to the
degree of interaction between age and alcohol on cognition, some studies have found adverse effects of alcohol on the CNS in older individuals (e.g., Mukamal et al., 2003; Pfefferbaum et al., 1992). For example, Pfefferbaum et al., (1992) found greater brain volume loss with age in alcoholics relative to controls. In addition, some studies have found an association between heavy alcohol use and risk of dementia (e.g., Mukamal et al., 2003). However, a number of studies have found the opposite, namely, that moderate alcohol use may facilitate successful cognitive aging (e.g., Bond et al., 2003; Stampfer, Kang, Chen, Cherry, & Grodstein, 2005), and may be protective against dementia (e.g., Deng et al., 2006; Luchsinger, Tang, Siddiqui, Shea, & Mayeux, 2004; Peters, Peters, Warner, Beckett & Bulpitt, 2008). Regardless, this evidence, alongside the collective evidence of potentially adverse CNS effects of the numerous co-morbid conditions that are prevalent in normally aging individuals, highlights the importance of considering such factors when attempting to differentiate the etiology of cognitive deficits found in older HIV-infected individuals.

**The Combined Influence of Aging and HIV**

With recent advances in the treatment of HIV (i.e., more effective antiretroviral therapies), mortality rates in HIV have decreased, and the prevalence of older individuals living with HIV infection has steadily increased (Centers for Disease Control and Prevention, 2009). Moreover, the number of later-life HIV infections has also increased, possibly due in part to delayed diagnosis or due to unsafe sexual practices (el-Sadr & Gettler, 1995; Zablotsky & Kennedy, 2003). In 2007, HIV individuals who were aged 50 and over accounted for 17% of new HIV/AIDS
diagnoses, and 28% of individuals living with HIV/AIDS, a number which has increased from 17% in 2001 (Centers for Disease Control, 2009). Although controversy exists with regard to the impact of aging on HIV disease outcomes, a number of studies have found that, in general, older HIV-infected individuals tend to have a longer overall duration of HIV-disease, greater exposure to antiretroviral medications, more rapid progression of HIV-disease, a poorer immunological response to combination antiretroviral therapy (cART), and a shorter mean time from diagnosis to death than their younger HIV-infected counterparts (Adler et al., 1997; Cherner et al., 2004; Goetz, Boscardin, Wiley, & Alkasspooles, 2001; Grabar et al., 2004; Operskalski et al., 1995; Phillips et al., 1991; Valcour et al., 2004).

Recent studies have also revealed evidence of greater neural damage in older HIV infected adults, relative to that found in normal aging and in younger HIV infected counterparts. For example, Ernst and Chang (2004) found greater age-dependent abnormalities in the frontal white matter (e.g., elevation of glial markers), and basal ganglia (e.g., neuronal damage or loss) in HIV-infected adults relative to seronegative controls. Research has also found evidence for an association between age and increased neuropathological burden (e.g., amyloid beta; Gelmen & Schuenke, 2004), and smaller frontal and temporal lobe volumes (Jernigan et al., 2005) in HIV-infected adults. It has also been posited that the combined effects of aging and HIV infection may lead to Alzheimer’s disease (AD)-like changes in the CNS. For example, Valcour et al. (2004) found a significant association between Apolipoprotein E epsilon 4 (APOEε4) and dementia among older HIV-infected patients that was not present among younger HIV-infected patients. However, this association has not
consistently been observed (e.g., see Dunlop et al., 1997). In addition, abnormal levels of CSF beta amyloid and tau concentrations have been found in HAD, which were similar to those found in AD patients, although a specific age-association was not determined (Brew, Pemberton, Blennow, Wallin, & Hagberg, 2005). Moreover, pathologies commonly found in AD and aging (e.g., amyloid plaques) have also been found in the brains of HIV-infected individuals (e.g., Achim et al., 2009; Green et al., 2005).

As both HIV infection and normal aging have been independently established as risk factors for cognitive decline and may share similar underlying neuropathological features, it has been posited that given the dual burden of both age and HIV infection, that older individuals with HIV infection may be at even greater risk of developing cognitive impairment than their younger HIV-infected counterparts (Becker, Lopez, Dew & Aizenstein, 2004; Cherner et al., 2004; Ettenhofer et al., 2009; Valcour et al., 2004). In fact, Valcour et al. (2004) reported a three-fold increased risk of HAD in older HIV infected individuals (i.e., over 50 years of age) relative to younger HIV-infected individuals, even when taking into account other demographic factors, HIV disease severity, psychiatric comorbidities, and cART use. Moreover, older HIV-infected individuals with more advanced disease (i.e., detectable CSF viral load, lower CD4 counts) may be at even greater risk for neurocognitive impairment (e.g., Cherner et al., 2004; Valcour et al., 2004).

However, while age- and HIV-associated neurocognitive decline has been well documented in the literature (e.g., Kissel, Pukay-Martin & Bornstein, 2005; van Gorp et al., 1994), the possible synergistic effects of age and HIV disease status on
neuropsychological functioning in HIV infection has been less well established. Although the effects of HIV and aging on neurocognition vary widely, some studies have revealed evidence of interactive and/or additive effects of aging and HIV infection. For example, Hardy et al. (1999) found a significant age by disease stage interaction when examining age-group differences in cognition in HIV-infected adults with AIDS versus HIV-infected adults without AIDS. Specifically, they found that older individuals (i.e., > 50 years old) with AIDS had a higher rate of cognitive impairment relative to the other group. Moreover, 87% of the older AIDS patients performed in the impaired range on a number of neuropsychological tests relative to normative comparison group data. As these findings were unrelated to other disease characteristics (e.g., CD4 count), they were interpreted as concomitant effects of aging and HIV disease rather than HIV disease stage alone.

With regard to specific cognitive domains, research has found that older adults with HIV infection may be more susceptible to impairment in executive functions, attention, information processing speed, and episodic memory (e.g., Cherner et al., 2004; Sacktor et al., 2007; Wilkie et al., 2003; Woods et al., 2010). However, other studies have found minimal to no evidence of an interaction between HIV infection and aging on cognition (e.g., Hardy et al., 1999; van Gorp et al., 1994). The lack of consistent findings is likely reflective of a number of factors, including individual differences in HIV-associated cognitive impairment, co-morbid substance abuse and dependence, psychiatric factors (e.g., depression), age- and HIV-related medical problems, and methodological differences between studies (e.g., neuropsychological test battery used).
One of the greatest complexities inherent in research on HIV and aging is the ability to delineate HIV-associated neurological and neuropsychological sequelae from that which may develop as a consequence of normal healthy aging, while also considering the myriad of co-existing conditions that are common in older HIV-infected individuals and have been established as risk factors for neural damage and cognitive disturbances. As mentioned above, a number of co-morbid medical (e.g., cardio- and cerebrovascular disease, hepatitis C virus), psychiatric (e.g., depression), and substance use (e.g., alcohol and illicit drug use) disorders are common in older HIV-infected individuals, have been established as independent risk factors for cognition, and may further complicate the course of HIV infection (e.g., Kilbourne et al., 2001) in older HIV-infected individuals. Only a few studies have addressed these co-morbidities within older HIV-infected adults specifically, and limited data is available with regard to incidence and prevalence rates of these conditions in older HIV-infected individuals. However, it is nonetheless important to consider these potential adverse neuropsychological effects that these co-morbid conditions may have in this population.

**Cerebro- and cardiovascular disease, HIV infection, and aging.** As individuals with HIV infection grow older, they may become more susceptible to a number of general age-related medical conditions. For example, medical conditions such as cerebro- and cardiovascular disease are common in older HIV infected individuals, possibly in part due to cART-induced metabolic changes (e.g., Bergersen, Schumacher, Sandvik, Brun, & Birkeland, 2006; Mary-Krause et al., 2003), and may interact with HIV disease to cause adverse effects on the CNS. Moreover,
cardiovascular disease has been demonstrated as a leading cause of non-HIV-related
death in HIV-infected individuals with advanced disease (i.e., AIDS; Sackoff, Hanna,
Pfeiffer & Torian, 2006). Research has demonstrated that older individuals with HIV
infection have greater prevalence rates of a number of general medical conditions
relative to younger HIV infected individuals. A three-site study including 881 HIV-
infected individuals enrolled from 1999-2000 (Kilbourne et al., 2001) examined the
prevalence rates of thirteen different medical conditions in older versus younger HIV-
infected individuals, and found that older individuals were more likely to experience
co-morbidities such as hypertension, hyperlipidemia, diabetes, myocardial
infarction/coronary artery disease, congestive heart failure, peripheral vascular
disease, stroke, and non-HIV-related cancers. Of these aforementioned medical
factors, hypertension, hyperlipidemia, and diabetes showed the highest prevalence
rates in the older HIV-infected individuals (i.e., 33%, 22%, and 15%, respectively;
Kilbourne et al., 2001).

Recent studies have revealed evidence of vascular disease and associations
between vascular disease and cognitive impairment in older HIV-infected individuals.
As mentioned above, white matter lesions are common in older adults, and are often
associated with vascular diseases such as hypertension and diabetes (Basile, et al.,
2006; Ovbiagele & Saver, 2006). It may be, given the prevalence of vascular disease
in both HIV-infected individuals and in normal aging, that the additional burden of
aging in the setting of HIV infection may lead to greater vascular neural damage. For
example, McMurtray, Nakamoto, Shikuma, and Valcour (2007) found greater
evidence of cerebral damage consistent with vascular disease (e.g., white matter
lesions) in older HIV infected individuals relative to younger HIV-infected counterparts, which was associated with higher mean systolic blood pressure and not with HIV disease characteristics (e.g., viral load, current and nadir CD4 count).

Significant associations between vascular risk factors and cognitive impairment have also been demonstrated in older HIV-infected adults (e.g. Becker et al., 2009; Foley et al., 2010; Valcour et al., 2006). For example, data from the Hawaii Aging with HIV Cohort (HAHC; Valcour et al., 2006) demonstrated an association between increasing insulin resistance levels and increasing severity of cognitive impairment that was more prominent in middle and older aged individuals. Becker et al., (2009) examined the effects of cardiovascular risk factors and HIV infection on cognition in a sample of middle to older aged individuals (i.e., over 40; mean age = 48.4), and found a significant association between abnormal levels of coronary artery calcification (i.e., a measure of cardiac integrity thought to be evidence of adverse effects of cerebrovascular disease on the brain), and poorer psychomotor speed in the HIV-infected individuals. Foley et al. (2010) further examined the differential impact of age and cerebrovascular risk factors (i.e., diabetes and hypertension) on individual cognitive domains and found a significant association between the presence of cerebrovascular risk factors and slower processing speed, even after controlling for age effects. Moreover, they found that individuals with untreated cerebrovascular risk factors showed greater detriments in cognitive domains including processing speed, executive functions, and learning and memory relative to those with controlled conditions (Foley et. al., 2010). Collectively, these studies highlight the importance
considering the potential influence of vascular disease on the cognitive performance of older HIV-infected adults.

**Hepatitis C Virus (HCV), HIV infection, and aging.** Given the aforementioned independent effects of HCV (e.g., Forton et al., 2001; Perry et al., 2008; Hilsabeck et al., 2002; Hilsabeck et al., 2003) and the potential additive effects of HIV/HCV co-infection (e.g., von Giesen et al., 2004; Martin et al., 2004; Hilsabeck et al., 2005) on the CNS and cognition, it is possible that the concomitant burden of aging may confer additional risk for disease progression (both liver disease and HIV) and cognitive impairment in older individuals co-infected with HIV and HCV. To my knowledge, no studies have directly examined the concomitant effects of HIV, HCV, and aging on cognition. However, given the abundant amount of research that has demonstrated effects of HIV/HCV co-infection on cognition, this is an important area to target for future research, as HCV is associated with increased morbidity and mortality among HIV infected individuals, possibly due to factors including aging, antiretroviral toxicity, and alcohol use (den Brinker et al., 2000; Sulkowski, Thomas, Chaisson, & Moore, 2000).

**Depression, HIV infection, and aging.** Advancing age has been demonstrated to be a risk factor for depression in HIV infection (e.g., Justice et al., 2004), with one epidemiological study estimating that approximately 44% of older HIV-infected individuals report depressive symptomatology, which was comparable to the rates found in younger HIV-infected individuals (i.e., 47%; Kilbourne et al., 2001). Evidence has also found that while rates of depression in HIV-infected individuals remain prevalent with advancing age, prevalence rates declined with age in
seronegative comparison groups (e.g., Justice et al., 2004; Rabkin, McElhiney, & Ferrando, 2004). Although the subtle independent adverse effects of depression on cognitive functioning (e.g., Austin et al., 1992; Cassens, Wolfe, & Zole, 1990) and the independent associations between HIV infection (e.g., Reger et al., 2002) and aging (e.g. Wilson et al., 1997) and cognitive decline have been well established, it remains unclear to what extent these factors interact with each other to produce neural damage and cognitive impairment. While no studies have addressed this issue directly, those that have accounted for depressive disorders as potential risk factors of cognitive dysfunction have suggested that depression may not contribute to significant cognitive dysfunction in older, HIV infected individuals (e.g., Cherner et al., 2004), which is consistent with prior research (e.g., Cysique et al., 2007). Nonetheless, further research in this area is warranted, as older adults with HIV infection and more depressive symptoms have been shown to be less adherent to their HIV treatment regimens (e.g., Catz, Heckman, Kochman, & Dimarco, 2001), which may adversely affect disease outcome and quality of life.

**Alcohol and substance use disorders, HIV infection, and aging.** As much of the extant literature on drug use, HIV infection, and cognition has focused primarily on cognitive functioning in younger adults, little is known of the effects of drug use and HIV infection in older individuals. However, alcohol and substance use disorders are also found in older HIV infected individuals, and may also confer adverse effects on brain structure and function in this population. Preliminary evidence has suggested that the rates of alcohol use disorders (e.g., alcohol abuse) in older, HIV infected individuals may be equally as prevalent as in younger HIV-infected individuals (e.g.,
Hinkin, Castellon, Atkinson, & Goodkin, 2001). For example, data from the Veterans with HIV/AIDS 3 Site Study (VACS3) reported that older adults with HIV infection had comparable rates of at-risk alcohol use (i.e., \( \geq 10 \) on the Alcohol Use Disorders Identification Test) relative to their younger counterparts (i.e., 18% versus 22%, respectively; Kilbourne et al., 2001). Given that all three factors have been established as risk factors for cognitive impairment, it may be that the burden of all three conditions may confer additive or synergistic effects on cognitive functioning. However, to my knowledge, no studies have directly examined the combined effects of alcohol, age, and HIV infection on cognition. Thus, research in this area is needed, as alcohol has been associated with more rapid HIV disease progression (e.g., Samet et al., 2007) and understanding the effects of alcohol in the older HIV infected population would aid in the development of more effective treatment strategies for the cognitive sequelae that may result from alcohol use in older HIV-infected adults.

Advancing age may also be a risk factor for substance use problems (Justice et al., 2004). For example, evidence from the Veterans with HIV/AIDS 3 Site Study (VACS 3) examined prevalence rates of common co-morbid conditions in a sample of 881 HIV infected individuals enrolled between July 1999 and July 2000, and found that 12% of the older HIV-infected individuals in their sample reported current illicit drug use (Kilbourne et al., 2001). At this time, to my knowledge, the direct effects of substance use on cognition in older HIV-infected individuals remains uncertain. However, it is plausible that substance use disorders may have an adverse effect on the CNS and cognition in older, HIV-infected individuals, given the aforementioned evidence of additive effects of substance use (e.g., methamphetamine) and HIV
infection on the CNS (e.g., Carey et al., 2006; Chang et al., 2005; Nath et al., 2002; Rippeth et al., 2004; Taylor et al., 2004). In addition, and of clinical importance, drug use in older HIV infected adults may be associated with declines in IADLs (e.g., poorer medication adherence; Ettenhofer, 2009), and along with cardiovascular disease, has been identified as a leading cause of non-HIV-related death in individuals with AIDS (i.e., Sackoff et al., 2006).

**Neurodegenerative disorders, HIV infection, and aging.** Also of concern when evaluating neuropsychological functioning in older HIV infected individuals is the presence of coexisting neurodegenerative disorders, which may hinder the ability of correctly identifying the etiology of HIV associated cognitive impairment (Skiest, 2003). Some have posited that older HIV-infected individuals may be at greater risk for neurodegenerative disorders such as Alzheimer’s disease (Valcour & Paul, 2006), as HIV infection may lower the threshold for the neurological and neuropsychological damage from such risk factors in older adults. This has been found in other neurodegenerative disorders, where the co-existence of certain conditions (e.g., cerebral infarction and Alzheimer’s disease) appears to lower the threshold for the clinical presentation of dementia (e.g., Snowdon et al., 1997). As mentioned above, recent evidence has found similar pathological features in both HIV infection and Alzheimer’s disease, including abnormal brain beta-amyloid deposition (Green et al., 2005), and increased intraneuronal accumulation of amyloid plaques (Achim et al., 2009). Moreover, research has demonstrated a potential association between an APOEε4 allele and HAD, which is also found in Alzheimer’s disease (Cordor et al., 1993). This preliminary evidence highlights an area of research that is in need of
further examination, as the older HIV-infected population is increasing, and an understanding of the additive or synergistic effects of aging, HIV and neurodegenerative disorders is needed in order to determine the etiology of cognitive impairment in older HIV-infected individuals and to provide the most effective treatment.

Collectively, evidence suggests that a number of co-morbid medical, psychiatric, and substance use disorders are prevalent independently in both normal aging and HIV, and are associated to some degree with cognitive impairment. Thus, it may be that the combined effects of such co-morbid risk factors, HIV infection, and aging on HIV disease progression, neuropsychological functioning, and everyday functioning may be even more detrimental than the effects of either risk factor alone, or in conjunction with either HIV infection or aging alone. Thus when examining cognition in older, HIV-infected individuals, it is important to determine the extent to which the aforementioned conditions (i.e., medical, psychiatric, and substance use disorders) contribute to cognitive decline in older HIV-infected individuals. Such research may ultimately aid in the identification and diagnoses of cognitive disorders in older HIV-infected individuals and the development of more effective treatment strategies that may ultimately improve their overall quality of life.

From a clinical standpoint, research on the effects of aging and HIV on cognition in older adults with HIV infection is of considerable importance, as older HIV-infected individuals with cognitive impairment (e.g., executive dysfunction, memory impairment) may also be at greater risk for declines in everyday functioning. For example, evidence has shown that while older HIV-infected adults demonstrate
better medication adherence than their younger counterparts, those that are cognitively impaired were more likely to have difficulties with adherence than older HIV-infected adults who were not cognitively impaired (Hinkin et al., 2004). In addition, Ettenhofer et al. (2009) found a significant relationship between poorer adherence and neurocognitive impairment in older HIV-infected adults that was not evidenced in the younger HIV-infected sample, and could not be better explained by confounding factors, including alcohol and drug problems, depression, and regimen complexity. Given the prevalence of cognitive impairment in older HIV-infected individuals, and the adverse consequences that these cognitive deficits may impose on daily functioning (e.g., poor medication adherence), more research is clearly needed in order to refine treatment strategies in order to improve overall quality of life in older HIV-infected individuals.

**Verbal Fluency**

Research has found verbal fluency deficits in both HIV infection (e.g., Iudicello et al., 2007; Iudicello et al., 2008; White et al., 1997) and in normal aging (e.g., Kozora & Cullum, 1995; Tomer & Levin, 1993). Verbal fluency requires rapid, self initiated search and retrieval from lexico-semantic stores to orally generate words beginning with a particular letter (i.e., letter fluency) or belonging to a specific semantic category (i.e., category fluency). Both letter fluency and category fluency have been shown to be particularly sensitive to many different types of brain damage (e.g., Butters, Granholm, Salmon, Grant & Wolfe, 1987) and appear to be mediated by differential brain regions. Specifically, research has found that letter fluency may be
mediated primarily by frontal systems (Abrahams et al., 2003) while both frontal and
temporal regions may underlie category fluency (Pihlajamaki et al., 2000). As such,
optimal fluency performance, and category fluency performance in particular, may be
dependent on both the integrity of frontal systems and executive processes (i.e., search
and retrieval strategies) and temporal lobe networks and the semantic memory stores.

While most research on verbal fluency has examined performance by using the
total number of correct words generated on each task, recent research has begun to
examine the multifactorial nature of fluency tasks by examining qualitative aspects of
fluency performance. One widely used example of this approach is the work of
Troyer, Moscovitch, and Winocur (1997), who proposed a conceptual model of verbal
fluency deficits that suggested that optimal fluency performance depends in part on
two independent factors; namely, clustering and switching. In brief, clustering refers
to the generation of words within specific lexico-semantic subcategories and is viewed
as an automatic retrieval process associated with the integrity of semantic memory and
the medial temporal lobes (e.g., Tröster et al., 1998). Switching describes the ability to
disengage from one lexico-semantic cluster in order to search for, engage, and retrieve
words from another relevant cluster (Troyer et al., 1997), and is considered to be a
more controlled executive ability, commonly associated with frontal systems (e.g.,
Eslinger & Grattan, 1993; Ho et al., 2002). Research on clustering and switching in
neurodegenerative processes (e.g., Alzheimer's Disease, Parkinson’s disease) has
provided support for switching as a function of frontal lobe integrity and executive
systems (e.g., cognitive flexibility, and rule-guided, self-initiated processes), and
clustering as primarily mediated by temporal systems and semantic memory stores.
For example, Troyer et al. (1998a) found that, relative to healthy comparisons, both Alzheimer's Disease (AD) and Parkinson’s disease (PD) patients produced fewer total words on both letter and category fluency. However, across both fluency tasks, AD patients were consistently impaired with regard to cluster size while PD patients were consistently impaired on switching abilities relative to healthy comparisons. Collectively, these findings provide support for the association between cluster size and the integrity of semantic memory stores, which tend to be affected early in the course of AD (e.g., Hodges & Patterson, 1995), and switching as a function of self-initiated search and retrieval processes, which are a prominent feature of PD (Beatty, Staton, Weir, Monson, & Whitaker, 1989).

**Verbal Fluency in HIV**

Verbal fluency deficits are found in approximately 40% of HIV-infected individuals (Rippeth et al., 2004). In order to determine the underlying neurocognitive mechanisms of HIV-associated verbal fluency deficits and to examine whether HIV infected individual demonstrated a differential impairment on letter fluency versus category verbal fluency, I conducted a meta-analysis examining 37 studies of verbal fluency in HIV infection. Results revealed that HIV infection is associated with comparable deficits in both letter and category fluency (Iudicello et al., 2007). Specifically, when examining all studies that included either a measure of letter or category fluency, the category fluency deficits ($d = -0.36$) were slightly larger than those on letter fluency ($d = -0.20$). However, a more rigorous analysis of only those studies that included both letter and category paradigms revealed no statistically
significant differences between letter and category fluency. These findings could not be attributed to possible confounding variables, including age, education, and antiretroviral therapy. Considering these findings are consistent with recent meta-analyses of verbal fluency deficits in populations with compromised frontal systems (e.g., Henry & Crawford, 2004), it is likely that HIV-associated fluency deficits are reflective of abnormalities within the fronto-striatal systems and corresponding executive dyscontrol of search and retrieval from lexico-semantic memory stores. In support of this notion, Hestad et al. (1993) found a negative correlation between verbal fluency and caudate atrophy in HIV-infected individuals. Research has also demonstrated that the magnitude of HIV-associated fluency deficits also worsens with disease progression, with the largest magnitude of impairment evident in individuals with AIDS (Iudicello et al., 2007). Of direct clinical relevance, verbal fluency deficits have also been shown to be independently predictive of dependence in IADLs (Heaton et al., 2004; Woods et al., 2006a).

Consistent with the notion that verbal fluency deficits may reflect preferential disruption of fronto-striatal circuits and subsequent executive dyscontrol, research on clustering and switching in HIV infection suggests that HIV-associated verbal fluency deficits are primarily driven by impaired switching. For example, Milliken, Trepanier & Rourke (2004) compared clustering and switching performance in HIV-infected individuals with AIDS to HIV-infected individuals without AIDS and found that individuals with an AIDS diagnosis were impaired in switching but not clustering on both letter and category fluency relative to those without AIDS. Moreover, Woods et al. (2004) examined clustering and switching abilities on letter fluency in demented
and demographically similar non-demented HIV positive individuals and seronegative adults, and found that individuals with HAD switched significantly less during letter fluency relative to the other two groups, but generated comparable lexico-semantic cluster sizes. These results remained when demographic factors, mood symptoms, and HIV disease variables were considered as potentially confounding variables. In addition, the HAD group displayed a higher proportion of response errors relative to the other two groups, the majority of which were classified as intrusions. Collectively, Woods et al., (2004) interpreted these findings to suggest HAD-associated verbal fluency deficits may reflect inefficient rule-guided lexical-semantic search strategies, possibly reflective of underlying HIV-associated frontostriatal damage, rather than the integrity of lexical-semantic memory stores. This research is consistent with the switching impairments found in other degenerative processes characterized primarily by subcortical involvement (e.g., PD; Troyer et al., 1998a).

Given the existing research suggestive of impaired switching in HIV infection, I (Iudicello et al., 2008) aimed to further examine switching deficits in HIV infection by examining clustering and switching abilities on category verbal fluency (i.e., animal fluency). Moreover, I aimed to explore switching abilities when the demands to switch categories were more explicit by using an alternating fluency measure (i.e., D-KEFS Category Switching subtest; fruits and furniture). Participants included 97 HIV-infected individuals and 43 demographically comparable (i.e., age, education, estimated verbal IQ, ethnicity) seronegative comparison participants. Each participant was administered a standard category verbal fluency task (i.e., animal fluency) which was individually scored for clustering and switching according to Troyer’s model
(Troyer et al., 2000; Troyer et al., 1997), and the Category Switching subtest from the D-KEFs, which required individuals to switch back and forth between two different semantic categories (i.e., fruits and furniture), generating as many words as possible in 60 seconds.

First, I found that HIV infection was associated with poorer category fluency relative to their seronegative counterparts, which was consistent with our prior meta-analysis (Iudicello et al., 2007) that demonstrated small, but significant category fluency deficits in HIV infection. Moreover, on the category fluency test, HIV infection was associated with a mild impairment in switching abilities, but not clustering, suggesting that HIV infection may be associated with impairment in the search and retrieval processes rather than a degradation of the semantic store. In addition, when the switching demands became more explicit (i.e., D-KEFS Category Switching subtest), the HIV-associated category fluency deficits were exacerbated. Specifically, HIV-infected individuals made significantly fewer switches on the D-KEFS Category Switching paradigm relative to their seronegative counterparts (Cohen's $d = -0.84$), and to a greater degree than on the standard category verbal fluency task (Cohen's $d = -0.33$). Such research provides further support for the disproportionate impairment in switching rather than clustering in HIV infection and evidence for the involvement of frontal systems in category fluency performance.

With regard to the possible underlying mechanisms of switching performance in HIV-infected individuals, research has found generally small but significant correlations with standard clinical measures of executive functions, working memory, and semantic memory (Iudicello et al., 2008). Taken together, the existing research on
clustering and switching in HIV infection provides support for the notion that HIV-associated verbal fluency deficits are primarily driven by switching impairments and related cognitive abilities, possibly reflective of abnormalities within the frontostriatal networks.

**Verbal Fluency and Aging**

Research on verbal fluency deficits in healthy older adults has consistently demonstrated that older adults tend to produce fewer words than their younger counterparts on category fluency (e.g., Kozora & Cullum, 1995; Tomer & Levin, 1993). While the literature on letter fluency in older adults has been less conclusive, a meta-analysis of letter fluency in healthy adults across the lifespan also revealed significant age-associated decline on this task (Rodriguez-Aranda & Martinussen, 2006). Research on verbal fluency deficits in age related disorders (e.g., Alzheimer’s disease; Hodges, Salmon & Butters, 1992) has also provided support for the possible underlying neural and cognitive mechanisms of such deficits. Specifically, Hodges et al. (1992) found that category fluency is preferentially impaired relative to letter fluency in Alzheimer’s disease (AD), providing support for the notion that temporal systems, which tend to be more affected in AD, may underlie category fluency performance (Pihlajamaki et al., 2001) and frontal systems mediate letter fluency performance (Abrahams et al., 2003). Thus, it may be that age related decline on measures of verbal fluency are reflective of age related structural and functional brain changes, particularly in frontal-temporal semantic networks. Of clinical importance, verbal fluency performance has also been shown to be associated with everyday
functioning in healthy older adults, especially for individuals who live alone and are required to perform tasks that provide little environmental assistance (Cahn-Weiner, Boyle & Malloy, 2002).

Examination of clustering and switching in healthy older adults revealed different patterns for letter and category fluency with regard to clustering and switching (Troyer et al., 1997). Specifically, Troyer et al. (1997) found that, on category fluency, older adults (i.e., 60-89 years old) produced fewer words overall and switched less frequently relative to the younger participants (i.e., 18-35), but they generated similar cluster sizes. Thus, they concluded, and confirmed with correlational data, that switching performance is an important component of overall category fluency performance in this group. On letter fluency, there was no age-group difference for total word output or number of switches, however, the older group tended to produce larger cluster sizes on letter fluency than the younger participants, an effect that the authors concluded may be related to vocabulary size, as there were no significant associations between performance and other demographics (e.g., education, sex). They also found that optimal performance on letter fluency in both age groups was significantly associated with switching ability but not clustering, providing support for switching as a measure of frontal lobe functioning. Taken together, the literature on aging and fluency indicates that older age is associated with deficits in both letter and category fluency, and the category fluency impairment in older adults may be primarily reflective of impaired switching rather than a decrease in clustering ability.
Verbal Fluency, HIV Infection, and Aging

Although verbal fluency deficits are found independently in both HIV infection and natural aging, the existing literature on the combined effects of HIV and aging on verbal fluency is very sparse. Those studies that have included measures of fluency in their neuropsychological test batteries have found conflicting results, with some finding both letter (e.g., Hardy et al., 1999; Sactor et al., 2007) and category fluency (Hardy et al., 1999) deficits in older HIV-infected individuals relative to younger individuals with HIV, and some pre-cART studies showing no interaction between age and HIV infection on fluency measures (e.g., van Gorp et al., 1994). With regard to letter fluency, Sactor et al., (2007) examined letter fluency performance in 133 older (i.e., age ≥ 50) HIV-infected individuals and 121 younger (i.e., age 20-39) HIV-infected participants and found greater impairment in the older HIV-infected individuals relative to their younger counterparts. Hardy et al. (1999) examined category (i.e., animal) fluency performance in older HIV-infected participants (i.e., mean age = 44.5 years) versus younger HIV infected participants (i.e., mean age = 31.5 years), and demonstrated greater impairment in older HIV-infected participants. These differences were greatest in the adults with AIDS relative to the HIV-infected adults without AIDS. However, neither of these studies included a seronegative comparison group, thus it was not possible to determine the additive effects of HIV and aging.

To my knowledge, while studies have examined the independent HIV- and age-associated effects on clustering and switching, no studies have examined the
possible adverse combined effects of age and HIV infection on these component processes. Thus, I aim to extend our prior research demonstrating adverse effects of HIV infection on verbal fluency (Iudicello et al., 2007), and specifically switching abilities (Iudicello et al., 2008; Woods et al., 2004) by exploring the possible additive deleterious effects of aging and HIV infection on verbal fluency and its proposed component processes (i.e., clustering and switching).

I will focus on category (i.e., animal) verbal fluency for a number of reasons. First, an analysis of category verbal fluency will provide a valuable extension of my prior work with category fluency in HIV infection (i.e., Iudicello et al., 2007; Iudicello et al., 2008). Second, research has demonstrated a greater and more consistent effect of aging on category verbal fluency in older adults relative to letter fluency (e.g., Kozora & Cullum, 1995; Tomer & Levin, 1993). Third, Troyer et al.’s clustering and switching paradigm (Troyer, 2000; Troyer et al., 1997) is most psychometrically sound in category verbal fluency (i.e., many researchers argue that switching is collinear with letter fluency, given the strong correlations between these two indices, which are much smaller in category fluency). Lastly, given the alternate hypotheses that the co-effects of aging and HIV infection on cognition may resemble that of an Alzheimer’s disease-like process, and evidence that category verbal fluency is more impaired relative to letter fluency in this population (e.g., Henry, Crawford, & Phillips, 2004), category verbal fluency appears to be a more reliable task in order to evaluate this possibility. Such research will provide valuable insight into the cognitive profile of older HIV-infected adults, an area of research that has been largely neglected, but essential given the increasing prevalence of older, HIV-infected
individuals, and may ultimately lead to the development of more effective treatment strategies for cognitive rehabilitation purposes and improvements in overall quality of life.
II. Aims and Hypotheses

**Aim 1:** Clarify the effects of aging on HIV-associated category fluency impairment.

**Hypothesis 1:** As both aging and HIV infection have been independently and jointly associated with impairment on category fluency tasks, it is hypothesized that aging and HIV infection will confer additive adverse effects on overall fluency performance (i.e., a step-wise effect will be observed such that the level of fluency impairment would increase in an orderly fashion as the number of neurocognitive risk factors increased, with younger seronegative individuals producing the greatest number of words and older HIV-infected individuals producing the fewest number of words overall).

**Hypothesis 2:** Given the similar pathologies found in AD and aging (i.e., amyloid plaques), and the controversial hypothesis that the effects of aging and HIV may confer AD-like changes in the CNS, it is possible that the older HIV-infected individuals may show a pattern more similar to AD patients (i.e., comparable clustering and switching deficits reflective of both executive dysfunction and degradation of the semantic store). However, considering research demonstrating the similar underlying neurological abnormalities (e.g., frontostriatal damage), corresponding cognitive deficits (e.g., executive dysfunction), and category fluency switching impairment found independently in both HIV and aging, it is hypothesized that aging and HIV infection will confer additive adverse effects on switching (i.e., a step-wise effect will be observed such that older HIV-infected individuals will switch...
less often relative to the other groups), but no additive effects will be observed for clustering abilities.

**Hypothesis 3:** Given evidence to suggest that cognitive impairment, and specifically, category fluency performance declines with disease progression (i.e., nadir CD4 count and CSF viral load), it is hypothesized that switching abilities will be associated with more advanced disease in the older HIV-infected individuals.

**Aim 2:** To determine the underlying cognitive mechanisms of verbal fluency impairment in older HIV-infected individuals.

**Hypothesis 1:** Category verbal fluency switching will correlate with other well-validated measures of executive functions, working memory, and information processing speed (i.e., convergent validity) in older HIV-infected adults.

**Hypothesis 2:** Category verbal fluency switching will not be correlated with tests of semantic memory (i.e., Wide Range Achievement Test) in older HIV-infected adults (i.e., divergent validity).

**Hypothesis 3:** Category verbal fluency switching will show concurrent validity with letter fluency switching.

**Aim 3:** Examine category fluency switching deficits as a predictor of declines in instrumental activities of daily living (IADLs).

**Hypothesis 1:** Given research to suggest that switching impairment may reflect difficulties with controlled (i.e., “executive”) processes, which are associated with both HIV infection and aging, and have been associated with functional decline in
both conditions, it was hypothesized that poorer switching performance would be predictive of self-reported IADL dependence in older HIV-infected adults, independent of potential contributing factors (i.e., disease severity and psychiatric co-morbidity).
III. Methods

Participants

This study included 257 participants who were recruited from the general community and local HIV clinics and enrolled in NIH-funded studies conducted at the HIV Neurobehavioral Research Center (HNRC; HNRC #5P30MH62512; NeuroAIDS: Effects of Methamphetamine and HCV #5P01DA12065). Each participant was classified with respect to HIV serostatus (i.e., HIV+ and HIV-) and age (i.e., older ≥ 50 and younger < 40) into one of four groups (i.e., Older HIV+, Older HIV-, Younger HIV+, and Younger HIV-). This classification yielded 63 Older HIV+, 51 Older HIV-, 50 Younger HIV+, and 93 Younger HIV- participants. Each participant provided written, informed consent and was administered a standard measure of category (i.e., animal) fluency alongside a comprehensive neuropsychological and medical evaluation. HIV infection was indicated by enzyme linked immunosorbent assays (ELISA) and a Western Blot confirmatory test and HCV diagnoses were confirmed through detection of HCV IgG antibody in plasma by ELISA. Individuals were excluded if they met Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM-IV; American Psychiatric Association, 1994) criteria for substance dependence within six months of evaluation or who tested positive for illicit drugs (except marijuana) on a urine toxicology screen conducted on the day of testing were excluded. Additional exclusion criteria included a history of severe psychiatric (e.g., schizophrenia) or neurological (e.g., active CNS opportunistic infections, cerebrovascular accidents, seizure disorders, closed head injuries) illness, or an
estimated verbal IQ score less than 70 on the Wide Range Achievement Test, Revision 3 (WRAT-3 Revised; Wilkinson, 1993).

Demographic characteristics for the four groups are presented in Table 1. By nature of the study’s age classification system, the four groups differed in age \((p < 0.001)\), such that the two older groups were significantly older than the two younger groups, although the two older groups were comparable relative to each other \((p = 0.197)\), as were the two younger groups \((p = 0.539)\). The four groups did not differ from each other in terms of years of education, ethnicity, and sex (all \(ps > 0.10\)).

Table 2 displays the medical and HIV disease characteristics for the study participants. Significant differences between the four groups emerged for all of the medical conditions, including hepatitis C virus (HCV; \(p < 0.001\)), hypertension (HTN; \(p < 0.001\)), hypercholesterolemia \((p = 0.012)\), and diabetes mellitus (DM; \(p = 0.001\)). Specifically, while both the Older HIV+ and Older HIV- groups had a significantly greater proportion of individuals infected with HCV relative to the two younger groups \((ps < 0.05)\), the older groups had comparable proportions relative to each other \((p = 0.169)\), as did the younger groups \((p = 0.646)\). The Older HIV+ group had higher and slightly higher rates of HTN relative to the Younger HIV- \((p < 0.001)\) and Younger HIV+ \((p = 0.062)\) cohorts, respectively, although they did not differ from the Older HIV- group \((p = 0.128)\). Rates of HTN in the Older HIV- group were higher than both the Younger HIV+ \((p = 0.001)\) and Younger HIV- \((p < 0.001)\) cohorts. Finally, the two younger groups had comparable proportions of individuals with HTN \((p = 0.167)\).
Table 1. Demographic, neuropsychological, IADL, and psychiatric characteristics.

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>HIV+</th>
<th></th>
<th>Group^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (n = 93)</td>
<td>Older (n = 51)</td>
<td>Younger (n = 50)</td>
<td>Older (n = 63)</td>
</tr>
<tr>
<td>Demographic Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.2 (5.2)</td>
<td>56.8 (4.9)</td>
<td>32.8 (4.0)</td>
<td>58.2 (6.2)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.0 (2.2)</td>
<td>13.4 (2.3)</td>
<td>14.2 (1.9)</td>
<td>13.9 (2.6)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>68.8%</td>
<td>74.5%</td>
<td>62.0%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>66.7%</td>
<td>78.4%</td>
<td>62.0%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Neuropsychological Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP Impaired (%)</td>
<td>18.3%</td>
<td>24.5%</td>
<td>30.0%</td>
<td>42.9%</td>
</tr>
<tr>
<td>Estimated Verbal IQ^b</td>
<td>103.4 (10.1)</td>
<td>100.1 (12.0)</td>
<td>103.2 (8.7)</td>
<td>101.5 (11.7)</td>
</tr>
<tr>
<td>IADL Dependent (%)</td>
<td>7.5%</td>
<td>15.7%</td>
<td>14.0%</td>
<td>39.0%</td>
</tr>
<tr>
<td>Psychiatric Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Mood Disturbance (POMS)^c</td>
<td>41.0 (22.8, 73.3)</td>
<td>40.0 (17.0, 81.0)</td>
<td>54.0 (5.0, 15.5)</td>
<td>62.0 (46.8, 91.5)</td>
</tr>
<tr>
<td>Tension/Anxiety^c</td>
<td>8.0 (3.0, 12.0)</td>
<td>6.5 (2.0, 9.8)</td>
<td>9.0 (5.0, 15.5)</td>
<td>10.0 (6.0, 16.3)</td>
</tr>
<tr>
<td>Depression/Dejection^c</td>
<td>4.0 (1.0, 14.0)</td>
<td>4.0 (1.0, 18.0)</td>
<td>6.0 (2.0, 16.0)</td>
<td>9.0 (4.0, 17.0)</td>
</tr>
<tr>
<td>Anger/Hostility^c</td>
<td>3.5 (0.8, 11.3)</td>
<td>4.5 (0.0, 10.7)</td>
<td>4.0 (1.0, 10.0)</td>
<td>5.0 (2.0, 11.0)</td>
</tr>
<tr>
<td>Vigor/Activation^c</td>
<td>17.0 (13.0, 22.0)</td>
<td>17.0 (9.3, 23.5)</td>
<td>15.0 (7.0, 22.5)</td>
<td>14.0 (8.0, 19.0)</td>
</tr>
<tr>
<td>Fatigue/Inertia^c</td>
<td>4.0 (1.8, 10.0)</td>
<td>5.5 (1.3, 12.5)</td>
<td>8.0 (2.5, 12.5)</td>
<td>10.5 (5.3, 16.8)</td>
</tr>
<tr>
<td>Confusion/Bewilderment^c</td>
<td>5.0 (2.0, 9.0)</td>
<td>4.0 (2.0, 9.8)</td>
<td>6.0 (3.0, 11.0)</td>
<td>8.0 (5.0, 13.0)</td>
</tr>
</tbody>
</table>

Note. Means (standard deviations) unless otherwise noted. IADL = Instrumental Activities of Daily Living; NP = neuropsychological performance; WRAT = Wide Range Achievement Test; POMS = Profile of Mood States; ^p < 0.05; ^Based on the Reading subtest from the Wide Range Achievement Test, Revision 3; ^Median (interquartile range).
<table>
<thead>
<tr>
<th></th>
<th>HIV- Younger (n = 93)</th>
<th>HIV- Older (n = 51)</th>
<th>HIV+ Younger (n = 50)</th>
<th>HIV+ Older (n = 63)</th>
<th>p</th>
<th>Groupa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C Virus (% infected)</td>
<td>5.1%</td>
<td>37.5%</td>
<td>7.3%</td>
<td>25.0%</td>
<td>&lt;0.001</td>
<td>Y = Y* &lt; O = O*</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>5.4%</td>
<td>39.2%</td>
<td>12.0%</td>
<td>25.8%</td>
<td>&lt;0.001</td>
<td>Y* = Y* = O* ; Y* &lt; O*</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>2.2%</td>
<td>5.9%</td>
<td>10.0%</td>
<td>16.1%</td>
<td>0.012</td>
<td>Y* &lt; Y* , O*</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>4.3%</td>
<td>9.8%</td>
<td>0.0%</td>
<td>17.7%</td>
<td>0.001</td>
<td>Y* &lt; O* , O* ; Y* &lt; O*</td>
</tr>
<tr>
<td><strong>HIV Disease Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Infection (years)</td>
<td>-----</td>
<td>-----</td>
<td>4.6 (4.5)</td>
<td>10.7 (6.5)</td>
<td>&lt;0.001</td>
<td>Y* &lt; O*</td>
</tr>
<tr>
<td>Proportion with AIDS (%)</td>
<td>-----</td>
<td>-----</td>
<td>32.0%</td>
<td>71.0%</td>
<td>&lt;0.001</td>
<td>Y* &lt; O*</td>
</tr>
<tr>
<td>Proportion on ARVs (%)</td>
<td>-----</td>
<td>-----</td>
<td>37.5%</td>
<td>76.7%</td>
<td>&lt;0.001</td>
<td>Y* &lt; O*</td>
</tr>
<tr>
<td>Nadir CD4 b (cells/µl)</td>
<td>-----</td>
<td>-----</td>
<td>282.0 (170.3, 463.5)</td>
<td>153.0 (50.0, 227.0)</td>
<td>&lt;0.001</td>
<td>Y* &gt; O*</td>
</tr>
<tr>
<td>Current CD4 b (cells/µl)</td>
<td>-----</td>
<td>-----</td>
<td>432.0 (273.5, 623.5)</td>
<td>419.0 (271.0, 596.8)</td>
<td>0.564</td>
<td>-----</td>
</tr>
<tr>
<td>Plasma HIV RNA b (log_{10})</td>
<td>-----</td>
<td>-----</td>
<td>3.9 (2.6, 4.7)</td>
<td>2.6 (1.7, 2.9)</td>
<td>&lt;0.001</td>
<td>Y* &gt; O*</td>
</tr>
<tr>
<td>CSF HIV RNA b (log_{10})</td>
<td>-----</td>
<td>-----</td>
<td>2.2 (1.7, 3.1)</td>
<td>1.7 (1.7, 2.1)</td>
<td>0.017</td>
<td>Y* &gt; O*</td>
</tr>
</tbody>
</table>

Note. Means (standard deviations) of raw scores unless otherwise indicated; HIV = Human Immunodeficiency Virus; AIDS = Acquired Immune Deficiency Syndrome; ARVs = antiretroviral therapies; CD4 = Cluster of Differentiation 4; CSF = Cerebrospinal Fluid. a p < 0.05; b Median (interquartile range).
Both the Older and Younger HIV+ groups had higher rates of hypercholesterolemia relative to the Younger HIV- group ($p = 0.001$ and $p = 0.044$, respectively), and the Older HIV+ group had slightly higher rates of hypercholesterolemia relative to the Older HIV- group ($p = 0.080$). Comparable rates of hypercholesterolemia were found between the Older HIV- group and both the Younger HIV+ and Younger HIV- groups ($ps = 0.442$ and 0.225, respectively). No differences in rates of hypercholesterolemia were found between the Older and Younger HIV+ individuals ($p = 0.338$).

While the Older HIV+ group had higher rates of diabetes mellitus (DM) relative to the Younger HIV+ ($p = 0.002$) and Younger HIV- ($p = 0.006$) groups, the proportion of individuals within the Older HIV+ cohort with DM did not differ significantly from that found in the Older HIV- group ($p = 0.222$). The Older HIV- group also had a greater proportion of DM relative to the Younger HIV+ group ($p = 0.008$), although their rates did not differ from the Younger HIV- group ($p = 0.203$). Finally, the Younger HIV+ group had slightly more individuals with DM relative to their younger seronegative counterparts ($p = 0.061$).

As might be expected, the Older HIV+ group had a longer duration of disease and a greater proportion of individuals diagnosed with acquired immune deficiency syndrome (AIDS) relative to the Younger HIV+ group (both $ps < 0.001$). While the Older HIV-infected individuals did not differ from the Younger HIV-infected individuals in terms of their current cluster of differentiation 4 (CD4) lymphocyte count ($p = 0.564$), the Older HIV+ group had lower Nadir CD4 counts ($p < 0.001$).
relative to the Younger HIV+ group. A larger proportion of the Older HIV+ group was taking antiretroviral medications ($p < 0.001$), and had lower plasma ($p < 0.001$) and CSF ($p = 0.017$) HIV viral loads relative to their younger counterparts.

**Procedure**

*Category fluency test.* Category fluency was assessed using the Category Fluency task, which requires individuals to generate as many animals as possible within 60 seconds. Category fluency performance was indexed by total number of correct responses, mean cluster size, and the total number of switches and was scored according to the rules and criteria established by Troyer et al. (Troyer, 2000; Troyer et al., 1997). In brief, clusters were defined as successively generated words that belong to the same subcategories, which are organized by living environment (e.g., animals that live in Africa or Australia), human use (e.g., animals used as pets), and zoological categories (e.g., types of birds, pets). For example, if the words emu, kangaroo, kiwi, cat, dog, hamster were successively generated, they were scored as two separate clusters (i.e., Australian animals and pets). Cluster size was counted beginning with the second word in each cluster, and a mean cluster size was calculated for each participant. The switching score was indexed by the total number of times an individual was able to disengage from one semantic cluster and switch to another. Repetitions and errors (i.e., perseverations and intrusions) were included in the mean cluster size and switching scores as they were considered to be informative with regard to the cognitive processes underlying performance.
**Other neuropsychological tests.** The remaining neuropsychological test battery included the reading subtest from the WRAT-3 (Wilkinson, 1993) as a measure of pre-morbid verbal intelligence, a measure of letter fluency (i.e., Controlled Oral Word Association Test – FAS; Benton, Hamsher, & Sivan, 1994), as well as measures designed to assess neurocognitive domains including speed of information processing, attention/working memory, executive functioning, learning, memory, and motor skills. The neuropsychological tests that were included in each domain are listed below:

1. **Speed of Information Processing:** Trail Making Test Part A (Army Individual Test Battery, 1944; Heaton, Grant & Matthews, 1991), Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol and Symbol Search (Heaton, Taylor, & Manly, 2002; The Psychological Corporation, 1997), Stroop Color Naming (Golden, 1978);
2. **Attention/Working Memory:** Paced Auditory Serial Addition Test (PASAT; Diehr, Heaton, Miller, & Grant, 1998; Gronwall, 1977; Gronwall & Sampson, 1974), WAIS-III Letter Number Sequencing (Heaton et al., 2002; The Psychological Corporation, 1997);
3. **Executive Functioning:** Halstead Category Test (Heaton et al., 1991; Reitan & Wolfson, 1993), Wisconsin Card Sorting Test-64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000) Perseverative Responses, Trail Making Test Part B (TMT-B; Army Individual Test Battery, 1944; Heaton et al., 1991), Stroop Interference (Golden, 1978);
4. **Learning:** Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998) Total Trial 1-3 Recall, Brief Visuospatial Memory Test-Revised
(BVMT-R; Benedict, 1997) Total Trial 1-3 Recall; (5) Memory: HVLT-R Percent Retained (i.e., trial 4 divided by the higher of trials 2 or 3) (Benedict et al., 1998), BVMT-R Percent Retained (i.e., trial 4 divided by the higher of trials 2 or 3; Benedict, 1997); (6) Motor: Grooved Pegboard Dominant and Non-dominant hand (Heaton et al., 1991; Klove, 1963).

Raw scores from the measures listed above were converted to population-based z-scores for correlational analyses within the older, HIV infected sample. In order to derive an indicator of overall cognitive functioning for the four groups (i.e., proportion of individuals classified as NP impaired within each group), raw scores from each of the individual neuropsychological tests were converted to demographically (e.g., age, education) corrected T-scores and used to derive neuropsychological domain T-scores and a global neurocognitive T-score. A baseline global deficit score was computed for each individual to provide a summary index of each individual’s baseline level of cognitive impairment (Carey et al., 2004) and was computed by converting the demographically corrected T-scores on the individual neuropsychological test measures to deficit scores ranging from 0 (no impairment) to 5 (severe impairment). The following conversions were used to convert T-scores into deficit scores: $> 40T = 0; 39T - 35T = 1; 34T - 30T = 2; 29T - 25T = 3; 24T - 20T = 4; \leq 19T = 5$. The deficit scores were then averaged to derive the GDS. A cut-off score of 0.5 was used to classify individuals as neuropsychologically impaired, thus an individual who demonstrated a GDS greater than 0.5 (which corresponds approximately to the 16th percentile and a T-score of less than 40) was classified as neuropsychologically impaired (i.e., NP Impaired; Carey et al., 2004).
By this system, a greater proportion of individuals within the Older HIV+ group were classified as NP Impaired relative to the Older HIV- \( (p = 0.041) \) and Younger HIV- \( (p < 0.001) \) groups (See Table 1). Rates of neuropsychological impairment did not differ between the Older HIV+ and Younger HIV+ cohorts \( (p = 0.158) \). Lastly, the older HIV- cohort had comparable proportions of NP impairment relative to the Younger HIV+ \( (p = 0.538) \) and Younger HIV- \( (p = 0.388) \) groups, and the Younger HIV+ cohort had equal rates relative to their younger seronegative counterparts \( (p = 0.114) \). The four groups did not differ in terms of estimated premorbid intelligence (i.e., WRAT-3; \( p = 0.282 \)).

**Self-report questionnaires.** Participants also completed self-report measures assessing current mood and competency with instrumental activities of daily living (IADLs). Current mood was assessed using the Profile of Mood States (POMS; McNair, Loor & Droppleman, 1981), which is a 65-item, self-report measure of current (i.e. the week prior to evaluation) affective distress. Participants were asked to rate various adjectives (e.g., “unhappy”) on a five-point Likert-type scale ranging from 0 (i.e., “not at all”) to 4 (i.e., “extremely”). Scores for individual adjectives are grouped into six subscales (i.e., Tension/Anxiety, Depression/Dejection, Anger/Hostility, Fatigue/Inertia, and Confusion/Bewilderment) used to derive a total mood score (i.e., POMS Total Mood Disturbance), which was used for all analyses. Significant differences between the groups were found for overall affective distress, as well as for five out of the six subscales (all \( ps < 0.05 \)), with the exception of the anger/hostility scale \( (p = 0.765; \) See Table 1). Specifically, the Older HIV+ cohort endorsed significantly greater overall affective distress relative to the Older HIV- \( (p = \)
0.031) and Younger HIV- (\(p = 0.004\)) individuals, but did not differ significantly from the Younger HIV+ group (\(p = 0.206\)). No differences were found in terms of overall affective distress between the Older HIV- group and both the Younger HIV+ (\(p = 0.354\)) and the Younger HIV- (\(p = 0.890\)) cohorts, nor did the two younger groups differ from each other (\(p = 0.114\)).

Everyday functioning was measured using a modified version of the Lawton and Brody (1969) Activities of Daily Living Scale, which requires participants to self-rate their current and best levels of functioning with regard to 10 instrumental activities of daily living (i.e., IADLs) including Financial Management, Home Repair, Medication Management, Laundry, Transportation, Grocery Shopping, Shopping, Housekeeping (Cleaning), Cooking, and Telephone Use. Participants were classified as IADL dependent if they reported decline (i.e., current rating of functioning is lower than their best level of functioning) in two or more IADLs, (consistent with Heaton et al., 2004, who, upon examination of the distributions of 168 neuropsychologically normal individuals on this scale determined that increased dependence on two or more of the aforementioned areas of functioning was relatively rare, and occurred in fewer than 15% of those cases). Analyses regarding the predictors of IADL dependence were conducted in the Older HIV+ group only. Using this system, within the older HIV infected cohort, 39% (n=24) were classified as “IADL Dependent”, whereas 61% (n=37) were considered “IADL Independent”.

**Analyses**

Prior to analyses, the data were reviewed for outliers (e.g., data points > 3.0 standard deviations from the overall mean) and normality using the Shapiro-Wilk W
Test of normality. Given the non-normal distributions of some of the fluency variables (e.g., mean cluster size), non-parametric statistics were used for consistency. A post hoc power analysis demonstrated that the study sample would provide statistical power (i.e., > 0.80) to detect medium effect sizes, using a critical alpha of 0.05, based on the sample size \( N = 257 \).

Hypotheses 1 and 2 of Aim 1 exploring the additive effects of aging and HIV infection on category fluency and category fluency component processes (i.e., clustering, switching, perseveration and intrusion errors) were examined using a series of Jonckheere-Terpstra tests for ordered monotonic trends (Jonckheere, 1954; Terpstra, 1952) using a priori ordered alternatives. Given prior research suggesting an overall impairment in overall word output on semantic fluency tasks and on semantic fluency switching abilities in both HIV infection (e.g., Iudicello et al., 2008; Milliken et al., 2004) and normal aging (e.g., Troyer et al., 1997), the level of verbal fluency and switching performance was predicted to decrease from groups expected to be high on the primary criterion (i.e., Younger HIV-) to samples low on the criterion (i.e., Older HIV+). As research has demonstrated intact clustering abilities in both HIV (e.g., Iudicello et al., 2008; Milliken et al., 2004) and normal aging (e.g., Troyer et al., 1997) it was predicted that there would not be a similar additive pattern of decline for mean cluster size.

Further examination of verbal fluency performance differences between the groups was conducted using Wilcoxon Rank-Sum tests, given the non-normality of some of the fluency variable distributions (e.g., mean cluster size), and was restricted to comparisons involving the older HIV+ group only to reduce Type I error risk.
Effect sizes for group comparisons were performed using Cohen’s $d$ statistics, where $d$-values of 0.2, 0.5, and 0.8 correspond to small, medium, and large effect sizes, respectively (Cohen, 1988). In order to explore the effects of potentially confounding factors on performance, regression analyses were conducted using the four level aging and HIV grouping variable (i.e., Older HIV+, Younger HIV+, Older HIV-, Younger HIV-) as a predictor of fluency performance, while accounting for variables of interest (e.g., demographic, medical, and psychiatric characteristics) that differed between the groups. Due to the very few individuals in the younger groups with HCV infection relative to the older groups, analyses examining the potential HCV effects on fluency performance were restricted to the two older groups. Correlational and regression analyses were also used to explore Hypothesis 3 of Aim 1, namely, whether HIV-disease confounds (e.g., Nadir CD4 Count and plasma viral load) were associated with category fluency performance among the Older HIV+ individuals.

Correlational analyses (i.e., nonparametric Spearman’s rho correlation coefficient) were used to explore the underlying cognitive mechanisms of switching performance within the Older HIV+ cohort (i.e., Aim 2, Hypotheses 1 and 2). Furthermore, regression analyses were used to explore the cognitive domains that were significant predictors of switching performance.

A series of Jonckheere-Terpstra tests for ordered monotonic trends were also conducted for letter fluency (i.e., COWAT-FAS) and its component processes (i.e., clustering and switching, perseveration and intrusion errors) to determine whether category verbal fluency demonstrated concurrent validity with letter fluency (Aim 2, Hypothesis 3).
Logistic regression procedures were used to explore Aim 3, Hypothesis 1, which aimed to investigate the relationship between switching performance and functional outcomes (i.e., self-reported independence or dependence in IADLs) in the older, HIV-infected sample, alongside possible confounding psychiatric (e.g., current affective distress) or HIV-disease (e.g., duration of infection) characteristics that differ between the IADL Dependent ($N = 24$) and Independent groups ($N = 37$). Finally, a receiver-operating characteristic (ROC) curve and classification accuracy statistics were conducted to determine whether switching performance could predict IADL dependence in the older HIV infected cohort. Based on the ROC curve, a cut point was established that would provide the best sensitivity-specificity balance (Woods, Weinborn, & Lovejoy, 2003). The critical alpha was set to 0.05 for all analyses.
IV. Results

Effects of Aging on HIV-associated Category Fluency Impairment

Table 3 presents the means and standard deviations for the category fluency variables. Jonckheere-Terpstra tests were performed to test the hypothesis that the median scores on overall category fluency performance as well as category fluency component processes (i.e., clustering and switching) are ordered such that Older HIV+ < Younger HIV+ = Older HIV+ < Younger HIV-. Results from the Jonckheere-Terpstra analyses for overall Category Fluency performance (i.e., total number of animals produced) revealed a significant monotonic trend between the groups, indicating a significant orderly decrease in overall category fluency performance, with the worst performance evident in the Older HIV infected group (J-T statistic = 2.68; \( p = 0.004 \); See Figure 1). A follow-up linear regression using the four level aging and HIV grouping variable (i.e., Older HIV+, Younger HIV+, Older HIV-, Younger HIV-) as a predictor of performance revealed that the aging/HIV group effect on category fluency remained significant when potentially confounding psychiatric (i.e., POMS Total Mood Disturbance) and medical (i.e., hypertension, diabetes, hypercholesterolemia) characteristics that differed between the groups were considered (\( p = 0.007 \)). Due to the very few participants in the Younger HIV- (n = 3) and HIV+ (n = 3) groups with HCV, examination of the potential HCV-associated effects on fluency performance was conducted in the older groups only. Within both the Older HIV+ and HIV- groups, no differences were observed for overall category
Table 3. Category and letter fluency variables.

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>HIV+</th>
<th>p^a</th>
<th>Group^b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (n = 93)</td>
<td>Older (n = 51)</td>
<td>Younger (n = 50)</td>
<td>Older (n = 63)</td>
</tr>
<tr>
<td><strong>Category Fluency Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total correct (raw score)</td>
<td>22.1 (4.6)</td>
<td>20.5 (4.2)</td>
<td>21.3 (4.9)</td>
<td>18.7 (5.4)</td>
</tr>
<tr>
<td>Total switches (raw score)</td>
<td>10.7 (2.9)</td>
<td>9.3 (2.8)</td>
<td>10.3 (2.7)</td>
<td>9.0 (3.0)</td>
</tr>
<tr>
<td>Mean cluster size (raw score)</td>
<td>1.1 (0.6)</td>
<td>1.3 (0.6)</td>
<td>1.0 (0.5)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td><strong>Category Fluency Errors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Errors^c,d</td>
<td>0.0 (0.0, 1.0)</td>
<td>1.0 (0.0, 1.0)</td>
<td>0.0 (0.0, 1.0)</td>
<td>0.0 (0.0, 1.0)</td>
</tr>
<tr>
<td>Perseverations^c,d</td>
<td>0.0 (0.0, 1.0)</td>
<td>1.0 (0.0, 1.0)</td>
<td>0.0 (0.0, 1.0)</td>
<td>0.0 (0.0, 1.0)</td>
</tr>
<tr>
<td>Intrusions^c,d</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
</tr>
<tr>
<td><strong>Letter Fluency Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total correct (raw)</td>
<td>42.1 (10.6)</td>
<td>41.1 (11.5)</td>
<td>41.1 (10.5)</td>
<td>38.3 (12.9)</td>
</tr>
<tr>
<td>Total switches (raw score)</td>
<td>29.1 (7.8)</td>
<td>28.6 (9.2)</td>
<td>28.9 (7.2)</td>
<td>26.0 (8.4)</td>
</tr>
<tr>
<td>Mean cluster size (raw score)</td>
<td>0.38 (0.2)</td>
<td>0.37 (0.2)</td>
<td>0.33 (0.2)</td>
<td>0.39 (0.2)</td>
</tr>
<tr>
<td><strong>Letter Fluency Errors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Errors^c,d</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 3.0)</td>
<td>1.0 (0.0, 2.0)</td>
<td>1.0 (1.0, 3.0)</td>
</tr>
<tr>
<td>Perseverations^c,d</td>
<td>1.0 (0.0, 2.0)</td>
<td>1.0 (0.0, 2.0)</td>
<td>0.5 (0.0, 1.0)</td>
<td>1.0 (0.0, 2.0)</td>
</tr>
<tr>
<td>Intrusions^c,d</td>
<td>1.0 (0.0, 2.0)</td>
<td>1.0 (0.0, 1.0)</td>
<td>0.0 (0.0, 1.0)</td>
<td>0.0 (0.0, 1.0)</td>
</tr>
</tbody>
</table>

Note. Means (standard deviations) unless otherwise noted. HIV = Human Immunodeficiency Virus; ^a p-values reflect Jonckheere-Terpstra tests unless otherwise noted; ^b p < 0.05; ^c Median (interquartile range). ^d p-values reflect nonparametric Wilcoxon Rank-Sums tests.
fluency output between HCV infected individuals and those without HCV infection ($p_s > 0.10$).

![Category Fluency Total Correct](image)

**Figure 1.** Additivity effect of HIV infection and aging on category fluency overall performance.

Follow-up pair-wise comparisons between the Older HIV+ group relative to the other groups were then conducted to further examine the overall additivity effect on category fluency total word output. Results indicated that the Older HIV+ group produced fewer overall words on the category fluency test relative to the Older HIV- ($p = 0.038$, Cohen’s $d = -0.37$), Younger HIV+ ($p = 0.017$, Cohen’s $d = -0.51$), and Younger HIV- ($p < 0.001$, Cohen’s $d = -0.70$) groups. Error analyses revealed no significant overall differences between the four groups for perseverations, intrusions, or total errors on the category fluency test (all $p$’s $> 0.10$).

A similar, albeit trend-level, additive effect was found for the switching component of animal fluency, such that the best performance was seen in the Younger HIV- group (i.e., they switched more frequently) with the greatest switching deficits found in the older, HIV-infected participants (J-T statistic = 1.59; $p = 0.056$; See
Figure 2). This effect was not better explained by mood variables (i.e., POMS Total Mood Disturbance), and medical conditions (i.e., hypertension, diabetes, and hypercholesterolemia) that differentiated the groups. In addition, within both the Older HIV+ and HIV- groups, no group differences were found for switching performance between individuals with HCV relative to those without HCV (both ps > 0.10).

Follow-up pair-wise comparisons exploring the additivity effect observed for switching performance revealed that the Older HIV+ cohort switched less often relative to the Younger HIV+ and Younger HIV- groups ($p = 0.025$, Cohen’s $d = -0.51$; and $p < 0.001$, Cohen’s $d = -0.70$, respectively), although they performed comparably to the Older HIV- adults ($p = 0.473$, Cohen’s $d = -0.13$).

![Category Fluency Total Switches](image)

**Figure 2.** Additivity effect of HIV infection and aging on switching abilities.

Within the Older HIV+ group, correlational analyses of potentially confounding effects of HIV disease characteristics revealed no significant associations between HIV disease characteristics (i.e., duration of infection, current CD4 count,
and plasma and CSF HIV viral loads) and category fluency switching performance (all 
p’s > 0.10). Moreover, there was no group effect of current ARV treatment or AIDS 
within the Older HIV+ cohort (both ps > .10). Specifically, individuals with AIDS 
(N = 18) demonstrated comparable switching performance to those without AIDS 
(N = 44; p = 0.876) and those on ARVs (N = 46) performed similarly to those who 
were not currently on ARVs (N = 13; p = 0.949).

In contrast to the significant switching analyses, no significant effect of age 
and HIV was found for the category fluency clustering variable (i.e., J-T statistic = 
-0.94; p = 0.826; See Figure 3), indicating that the median levels of clustering did not 
decrease in an orderly fashion as did the other two variables of interest (i.e., category 
fluency total word output and switching).

**Figure 3.** Additivity effect of HIV infection and aging on mean cluster size.
Cognitive Mechanisms of Switching in Older HIV-infected Adults

Spearman’s Rho correlations between the category fluency switching variable, individual cognitive domains (i.e., attention/working memory, executive functioning, learning, memory, motor, semantic memory, and speed of information processing), were conducted within the Older HIV+ group to examine the cognitive correlates underlying switching performance within this cohort (See Table 4). Switching performance correlated strongly with the majority of the cognitive domains (i.e., attention/working memory, learning, and speed of information processing; Spearman’s Rho values ranging from 0.304 to 0.486; all \( p < 0.01 \)), with slightly smaller but significant associations with motor skills and memory (Spearman’s Rho = 0.304; \( p = 0.018 \) and Spearman’s Rho = 0.328; \( p = 0.010 \)) and a correlation with executive functioning at a trend level (Spearman’s Rho = 0.224; \( p = 0.082 \)). In contrast, switching performance was not significantly associated with semantic memory as measured by the WRAT-3 (Wilkinson, 1993; Spearman’s Rho = 0.182; \( p = 0.226 \)).

Regression analyses examining the cognitive predictors of switching revealed executive functions (\( p = 0.011 \)) and learning (\( p = 0.024 \)), as independent predictors of animal switching performance (adjusted \( R^2 = 0.27 \)).

Table 4. Correlations between category fluency switching and individual cognitive domains within the Older HIV-infected group (n = 63).

<table>
<thead>
<tr>
<th>Individual Cognitive Domains</th>
<th>Category Fluency Switching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s Rho</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>0.349</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>0.244</td>
</tr>
<tr>
<td>Learning</td>
<td>0.486</td>
</tr>
<tr>
<td>Percent Retained</td>
<td>0.328</td>
</tr>
<tr>
<td>Motor</td>
<td>0.304</td>
</tr>
<tr>
<td>Semantic Memory</td>
<td>0.182</td>
</tr>
<tr>
<td>Speed of Information Processing</td>
<td>0.345</td>
</tr>
</tbody>
</table>
A series of Jonckheere-Terpstra analyses were then conducted on letter fluency (i.e., COWAT-FAS; Benton, Hamsher, & Sivan, 1994) and its component processes (i.e., clustering and switching) in order to examine whether letter fluency and its component processes showed concurrent validity with the category fluency variables (Aim 2, Hypothesis 3). Analyses for overall Letter Fluency performance (i.e., total number of animals produced) revealed a slight monotonic trend between the four groups, with the worst performance evident in the Older HIV infected group (J-T statistic = 1.58; \( p = 0.057 \)). Follow-up pair-wise comparisons indicated that the Older HIV+ group produced fewer overall words on the letter fluency test relative to the Younger HIV- group (\( p = 0.032 \), Cohen’s \( d = -0.33 \)), although no other significant group differences in performance on overall letter fluency output were observed (all \( p \)’s > 0.10). Error analyses revealed no significant overall differences between the four groups for perseverations, intrusions, or total errors on the letter fluency test (all \( p \)’s > 0.10).

A similar slight monotonic trend was found for letter fluency switching, again with the Older HIV+ demonstrating the worst switching performance relative to the other groups (J-T statistic = 1.43; \( p = 0.076 \)). Follow-up analyses indicated that the Older HIV+ group switched significantly less than the Younger HIV- group (\( p = 0.024 \), Cohen’s \( d = -0.39 \)), and slightly less than both the Older HIV- (\( p = 0.095 \), Cohen’s \( d = -0.30 \)) and Younger HIV+ (\( p = 0.060 \), Cohen’s \( d = -0.39 \)) groups. Similar to the category fluency results, additivity analyses did not suggest an orderly trend in performance for letter fluency mean cluster size (J-T statistic = 0.694; \( p = 0.244 \)). Again, although overall findings suggested no differences between the four groups,
follow-up analyses were conducted to confirm the absence of group differences between the Older HIV+ group relative to the other groups on letter fluency mean cluster size ($ps > 0.10$).

Table 5 displays the associations between the letter and category fluency variables (i.e., total words generated, number of switches, and mean cluster size) within the Older HIV+ group. A greater overall number of words generated on the category fluency task was significantly associated with a greater number of words produced on the letter fluency task (Spearman’s Rho = 0.556, $p < 0.001$) and a greater number of switches on the letter fluency task (Spearman’s Rho = 0.561; $p < 0.001$). A greater number of switches on the category fluency task was significantly correlated with more overall words produced on the letter fluency task (Spearman’s Rho = 0.512, $p < 0.001$), and a larger number of overall switches on the letter fluency task (Spearman’s Rho = 0.587; $p < 0.001$). No significant correlations were found between category mean cluster size and the letter fluency variables (i.e., total word output, total number of switches, mean cluster size; all $ps > 0.10$) nor were there any significantly relationships found between the letter fluency mean cluster size and the category fluency variables (i.e., total word output, total number of switches, mean cluster size; all $ps > 0.10$).
Finally, correlational analyses were conducted within the Older HIV+ group to determine the contributions of the component processes (i.e., clustering and switching) on each task (i.e., letter and category fluency) to total overall output. Table 5 also displays the relationships between overall category fluency output and category fluency clustering and switching component processes. While a greater total number of words generated on category fluency was significantly related to more category fluency switches (Spearman’s Rho = 0.652; \( p < 0.0001 \)), total word output was unrelated to category fluency mean cluster size (Spearman’s Rho = 0.169; \( p = 0.178 \)). A greater number of category fluency switches was also associated with smaller mean cluster sizes on this task (Spearman’s Rho = -0.512; \( p < 0.001 \)). Table 5 also displays the correlations between letter fluency total word output and letter fluency component processes (i.e., clustering and switching). On letter fluency, better overall output was associated with a greater number of switches (Spearman’s Rho = 0.899; \( p < 0.001 \)) as well as larger mean cluster sizes (Spearman’s Rho = 0.489; \( p < 0.001 \)). The component processes of letter fluency (i.e., clustering and switching) were not significantly associated with each other (Spearman’s Rho = 0.146; \( p = 0.266 \)).

Table 5. Spearman’s Rho correlations between category fluency and letter fluency variables within the Older HIV+ cohort (n = 63).

<table>
<thead>
<tr>
<th>Category Fluency Variables</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Output [1]</td>
<td>-----</td>
<td>0.652*</td>
<td>0.169</td>
<td>0.556*</td>
<td>0.561*</td>
<td>0.161</td>
</tr>
<tr>
<td>Total Switches [2]</td>
<td>0.652*</td>
<td>-----</td>
<td>-0.512*</td>
<td>0.512*</td>
<td>0.587*</td>
<td>0.062</td>
</tr>
<tr>
<td>Mean Cluster Size [3]</td>
<td>0.169</td>
<td>-0.512*</td>
<td>-----</td>
<td>-0.111</td>
<td>-0.207</td>
<td>0.052</td>
</tr>
<tr>
<td>Letter Fluency Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Output [4]</td>
<td>0.556*</td>
<td>0.512*</td>
<td>-0.111</td>
<td>-----</td>
<td>0.899*</td>
<td>0.489*</td>
</tr>
<tr>
<td>Total Switches [5]</td>
<td>0.561*</td>
<td>0.587*</td>
<td>-0.207</td>
<td>0.899*</td>
<td>-----</td>
<td>0.146</td>
</tr>
<tr>
<td>Mean Cluster Size [6]</td>
<td>0.161</td>
<td>0.062</td>
<td>0.052</td>
<td>0.489*</td>
<td>0.146*</td>
<td>-----</td>
</tr>
</tbody>
</table>

* \( p < 0.001 \); otherwise non-significant.
Switching Performance as a Predictor of Functional Decline

Finally, poorer switching performance was examined in the Older HIV infected group as a predictor of declines in everyday functioning, while accounting for potentially confounding demographic, psychiatric, and HIV disease variables. The dependent variable of interest was a dichotomized IADL Independent/Dependent variable derived by totaling the number of activities for which an individual has declined (relative to their best level of functioning), and classifying individuals as IADL Dependent if they reported decline in two or more functional areas. This classification system yielded 24 IADL Dependent and 37 IADL Independent older HIV infected individuals.

The IADL Dependent and Independent samples were generally comparable with respect to most demographic (e.g., age, ethnicity, gender), medical (i.e., hepatitis C virus, hypertension, diabetes mellitus, and hypercholesterolemia) and HIV disease characteristics (e.g., AIDS status, Nadir CD4 lymphocyte count, current CD4 count, plasma and CSF viral loads) that may influence an individual’s everyday functioning abilities (all \( p > 0.10 \)). Nevertheless, the IADL Dependent group had slightly higher education levels (\( p = 0.087 \)) and longer durations of HIV infection (\( p = 0.082 \)). The IADL Dependent and Independent groups did not differ in rates of global neuropsychological impairment (\( p = 0.142 \)). Individuals classified as IADL Dependent endorsed significantly more affective distress (i.e., POMS Total Mood Disturbance; \( p < 0.001 \)).

Thus, a logistic regression was used to evaluate switching performance as a predictor of IADL dependence alongside years of education, current affective distress
(i.e., Total Mood Disturbance), and duration of HIV infection. Results revealed that switching performance was a significant independent predictor of dependence in instrumental activities of daily living ($p = 0.016$) in the Older HIV+ group, even when accounting for HIV disease characteristics (i.e., duration of infection), current affective distress (i.e., POMS Total Mood Disturbance), and years of education (overall model $\chi^2 = 33.5; p < 0.001$; See Table 6).

Finally, ROC analyses were conducted on the category fluency switching variable. Results revealed that switching scores were better than chance at classifying IADL dependence within the Older HIV+ cohort (area under the curve = 0.72, SE = 0.11, $p = 0.002$). Based on the ROC curve, a switching cutoff score (i.e., 7 switches) was derived that provided the optimal balance between sensitivity (0.54) and specificity (0.86). The overall hit rate was 73% with an odds ratio of 7.56 (95% CI = 1.08 - 1.73). The positive predictive power was 0.72, and the negative predictive power was 0.74.

### Table 6. Nominal logistic regression model predicting IADL dependence by category fluency switching, mood symptoms (i.e., POMS Total Mood Disturbance), duration of HIV infection, and education within the Older HIV+ cohort ($n = 63$).

<table>
<thead>
<tr>
<th>Criterion Variable</th>
<th>Predictor Variable</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADL Dependence</td>
<td>Category Fluency Switching</td>
<td>5.81</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>POMS Total Mood Disturbance</td>
<td>8.62</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Duration of HIV Infection</td>
<td>2.15</td>
<td>0.142</td>
</tr>
<tr>
<td></td>
<td>Years of Education</td>
<td>2.73</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Note. IADL = Instrumental Activities of Daily Living; POMS = Profile of Mood States; HIV = Human Immunodeficiency Virus.
V. Discussion

With recent advances in the treatment of HIV (i.e., more effective antiretroviral therapies), mortality rates in HIV have decreased, and the prevalence of older individuals living with chronic HIV infection has steadily increased (CDC, 2009). As both normal aging and HIV infection have been associated with neural injury (e.g., within frontostriatal regions; Ernst & Chang 2004; Jernigan et al., 2001) and have been established as independent risk factors for cognitive decline (e.g., Park et al., 2003; Rippeth et al., 2004), there is growing concern with regard to the neurological and neuropsychological sequelae that may result from the additional burden of both HIV and aging on the CNS. Research has found evidence of greater neural abnormalities with age in HIV-infected individuals, particularly within frontostriatal regions (Ernst & Chang, 2004; Jernigan et al., 2005). In addition, evidence of cognitive decline (e.g., reduced information processing speed, executive dysfunction, learning and memory impairment; Cherner et al., 2004; Sacktor et al., 2007; Wilkie et al., 2003) and associated declines in everyday functioning (e.g., Ettenhofer et al., 2009; Hinkin et al., 2004) has been observed in older HIV-infected individuals.

While preliminary research examining the combined effects of HIV and aging on neurocognitive functioning has demonstrated deleterious additive effects (e.g., prospective memory; Woods et al., 2010), the underlying mechanisms remain unclear. This current study sought to further explore the additive effects of HIV and aging on cognition by examining effects on category fluency and category fluency component processes (i.e., clustering and switching). Both aging and HIV infection have been
independently and jointly associated with category fluency impairment, which appears to be driven primarily by a deficiency in the executive processes involved in switching between semantic categories (e.g., inefficient encoding, search and retrieval strategies), possibly reflective of underlying frontostriatal damage, rather than an inability to generate sufficient cluster sizes. Given this evidence, it was hypothesized that the effects of HIV and aging together may confer additive adverse effects on category fluency, and that these effects would be most evident on switching performance. This study also aimed to explore the underlying cognitive mechanisms of switching abilities in older HIV infected adults, as well as the relationship between switching abilities and everyday functioning in this cohort.

Consistent with the primary hypotheses (Hypotheses 1 and 2 of Aim 1), results from this study showed adverse additive effects of HIV infection and aging on category verbal fluency. More specifically, significant additive effects were found for overall category fluency, with performance levels highest in the Younger HIV seronegative group and lowest in the Older HIV+ group. The Older HIV+ group produced significantly fewer words relative to each of the remaining groups (i.e., HIV-O, HIV+Y, HIV-Y; Cohen’s $d_s = -0.37, -0.51, $ and -0.70, respectively). Examination of the component processes of category fluency revealed a similar additive effect of HIV infection and aging on switching abilities (albeit at a trend level). While older HIV infected individuals switched significantly less often relative to the younger HIV+ and younger HIV- groups (Cohen’s $d_s = -0.46, and -0.59, respectively) they performed comparably to the older HIV- group (Cohen’s $d = -0.13$). Consistent with the proposed hypotheses (i.e., Hypothesis 2 of Aim 1), it does not appear that HIV and
aging confer additive effects on clustering. No step-wise additive effects were found for mean cluster size, and the older HIV+ group generated similar mean cluster sizes relative to each of the other groups.

Given the similar stair-step additive pattern of impairment observed for overall category fluency output and switching performance, but not clustering, it appears that the additive deleterious effects of HIV infection and aging may be preferentially driven by reduced switching rather than an impairment in clustering. Consistent with this notion, while research in healthy adults has demonstrated that both clustering and switching play a role in optimal category fluency performance (Troyer et al., 1997), only category fluency switching abilities were associated with greater overall performance, whereas clustering was not. This provides further evidence that the category fluency impairment observed within this older HIV infected cohort may reflect the additive burden of HIV infection and aging on the controlled (i.e., executive) processes involved in switching between semantic categories.

In addition, similar but slightly less pronounced additive effects were found for letter fluency (i.e., COWAT-FAS; Benton, Hamsher, & Sivan, 1994), whereby a slight step-wise additive effect was observed for both overall performance and switching, but not clustering, with the worst performance observed in the Older HIV+ cohort. Again, these results suggest that overall letter fluency impairment may also be driven by impairment in the executive components involved in switching, rather than clustering abilities. Consistent with this notion, prior research in both aging and HIV infection has suggested that deficient executive processes (e.g., self-initiated encoding, search, and retrieval strategies) may underlie both age- and HIV-associated category
fluency impairment (e.g., Iudicello et al., 2008; Troyer et al., 1997; Woods et al., 2004).

Results of this study suggest that category fluency impairment in older HIV infected adults is primarily driven by an inability to switch between clusters, which involves the ability to disengage from an exhausted semantic category, and then search for, and retrieve a different semantic category. As such, the concept of switching has been argued as somewhat ambiguous (Mayr, 2002) in the sense that a switching impairment may reflect a deficit in a number of different cognitive abilities, including the use of inefficient self-initiated search and retrieval strategies, including an inability to inhibit inappropriate responses, slowed retrieval, attention shifting, or mental flexibility. Error analyses have been suggested as one possible route to gain further insight regarding these underlying cognitive processes. For example, Woods et al. (2004) found a high proportion of letter fluency intrusion errors in a sample of HIV infected individuals with HAD, the majority of which coincided with a switch between phonemic clusters, a finding that they interpreted may be due to deficient lexicosemantic search strategies, as opposed to inefficient retrieval strategies or problems disengaging from an exhausted category.

Unfortunately, this study was not well suited to draw inferences with regard to the specific executive processes that may be driving the switching deficits. While results do provide evidence that the switching impairment is unlikely due to inefficient clustering, as the older HIV+ cohort generated similar cluster sizes to those of the other groups, it remains to be discovered which of the other underlying cognitive processes may be primarily responsible for the switching impairment. Unfortunately,
the very small proportion of individuals who made errors on category fluency precluded a more detailed error analyses. Prospective experimental studies should be designed to address these specific cognitive mechanisms that may underlie switching impairment in older HIV infected individuals. For example, examination of the time that elapses between words within clusters, relative to words that occur prior to, and following a switch, as well as a concurrent analysis of the semantic relatedness of the words within clusters and surrounding the switch, may provide useful information with regard to both the executive and semantic processes that may underlie switching performance, and may allow for a more accurate depiction of the switching deficits underlying category fluency impairment.

Despite the uncertainty with regard to specific processes involved in the executive components of category fluency switching, these results nonetheless provide overall support that the additive effects of aging and HIV infection on category fluency likely reflects a deficiency in the executive processes involved in switching. More generally speaking, the overall additive effects of HIV and aging on category fluency observed in this study are consistent with research demonstrating that older HIV infected individuals may be at increased risk for cognitive decline (e.g., Valcour et al., 2004), and may show greater cognitive impairment, particularly with regard to executive functioning abilities relative to individuals with either risk factor (i.e., older age or HIV infection) alone (e.g., Cherner et al., 2004; Sacktor et al., 2007). In addition, results coincide with preliminary evidence suggesting additive deleterious neurocognitive effects of HIV and aging on the executive components involved in prospective memory (ProM; Woods et al., 2010). Specifically, Woods et al., (2010)
found significant additive effects of HIV and aging on ProM performance, with the worst performance observed in the older HIV+ cohort. Importantly, on event based ProM tasks, the older HIV+ group performed particularly poorly on tasks where the cue-intention pairings were semantically unrelated (e.g., “When I show you a picture of a cow, snap your fingers”), and thus presumably may impose greater demands on strategic (i.e., executive) encoding and retrieval processes, relative to semantically related cue-intention pairings (e.g., “When I hand you a postcard, self-address it”), which may reflect more automatic cognitive processes. Thus, given research implicating the frontal systems with ProM (e.g., Simons, Schölvinck, Gilbert, Frith, & Burgess 2006), they concluded that the impairment on semantically unrelated cue-intention pairings in their older HIV infected cohort may reflect additive effects of HIV infection and aging on the executive components of ProM, which, although speculative, may also suggest a potential additive burden on frontostriatal circuits.

Consistent with the hypothesis that prominent executive dysfunction may underlie the cognitive impairment observed in older HIV infected individuals, and specifically switching impairment in this study, associations between individual cognitive domains suggested that switching impairment in this Older HIV+ cohort may be preferentially driven by executive dysfunction and learning deficits. While category fluency switching performance was indeed associated with a majority of the cognitive domains assessed (e.g., attention/working memory, executive functioning, motor, learning, memory, and information processing speed), which may argue for diffuse neurological damage and global neurocognitive impairment in older HIV infected individuals, evidence of domain specificity for executive functioning and
learning argues against this hypothesis. Despite the significant associations with the aforementioned cognitive domains, only executive functions and learning emerged as significant predictors of switching performance. This is consistent with prior research demonstrating executive dysfunction in both aging and HIV infected populations (e.g., Reger et al., 2002; Wilson et al., 1997), and with the profile of episodic learning and memory impairment in HIV infected individuals (e.g., Becker et al., 1995; Delis et al., 1995; Gongvatana et al., 2007). Broadly, the profile of learning and memory impairment observed in HIV infected individuals is similar to that found in subcortical dementias, whereby learning and recall of information is impaired, although recognition abilities are relatively spared. As far as episodic memory is concerned, this profile suggests impairment in the executive processes involved in the recall of information (e.g., self-initiated retrieval strategies), as performance is improved when the demands on such executive processes are minimized (e.g., on recognition tasks).

Recent research on the learning profile in HIV infection has also suggested that dysfunction in the executive processes involved in learning may play a significant role in HIV-associated learning and memory impairments (e.g., Gongvatana et al., 2007; Woods et al., 2005). For example, Woods et al. (2005) examined the use of effective organizational strategies (i.e., semantic clustering), which have been associated with frontal systems dysfunction (e.g., Baldo & Shimamura, 2002), during an episodic learning and memory task in HIV infection, and found that HIV infected individuals showed poorer use of efficient organizational strategies (i.e., semantic clustering) relative to healthy comparison subjects, which in turn was associated with poorer recall. Given this evidence in addition to significant correlations between better
episodic retrieval and better performance on tests of executive functions, they concluded that the episodic learning and memory impairment observed in their HIV infected cohort may reflect a deficiency in the executive control of encoding and retrieval abilities. Taken collectively along with results from this study, there is convincing evidence to suggest that the verbal fluency impairment observed in older HIV infected individuals is driven primarily by executive dysfunction, which may reflect underlying prefrontostriatal damage.

Results from this study also suggest that while executive functions may be particularly vulnerable to the effects of aging and HIV infection, that other cognitive domains, most notably semantic memory, may be relatively spared. Consistent across both fluency measures, no additive effect of HIV infection and aging was found for clustering performance, which has been linked to the integrity of the semantic memory stores and temporal lobe structures. In addition, the switching impairments observed in the Older HIV cohort were not significantly associated with a measure of semantic memory (i.e., WRAT-3 Reading). These results are consistent with the clustering and switching literature in both aging and HIV infection, which has demonstrated that while switching abilities are particularly affected, that clustering abilities may remain intact (Iudicello et al., 2008; Millkin et al., 2004; Troyer et al., 1997; Woods et al., 2004). In addition, this hypothesis is also supported by the aforementioned research in episodic learning and memory in HIV infection that only found minimal associations between the use of effective organizational strategies and measures of semantic memory.
Unfortunately, direct inferences with regard to the potential underlying neural circuitry driving the category fluency and category fluency switching impairment in this older HIV infected cohort cannot be drawn directly from this study. However, neuroimaging research and evidence from clinical populations regarding verbal fluency and its component processes (i.e., clustering and switching) may shed light on the potential underlying neural mechanisms underlying verbal fluency performance in older HIV infected individuals. Historically, category fluency has been closely associated with semantic memory and the medial temporal lobes, whereas letter fluency has been linked with executive functions and frontal lobe regions (e.g., Henry & Crawford, 2004; Moscovitch, 1994). However, recent meta-analyses have revealed evidence to suggest that while category fluency is indeed preferentially impaired in conditions known to target temporolimbic regions (e.g., focal temporal lesions; Henry & Crawford, 2004), letter and category fluency are comparably impaired in conditions characterized primarily by frontal systems damage (e.g., focal frontal lesions, Baldo & Shimamura, 1998; Henry & Crawford, 2004). In addition, imaging studies have found activation in the prefrontal cortex during semantic fluency tasks (e.g., Pujol et al., 1996). Collectively, this evidence suggests that while category fluency does depend, in part, on temporal lobe functioning and the integrity of the semantic store, frontal lobes may play a significant role in optimal category fluency performance, possibly reflective of the demands of rule-guided search and retrieval of lexical-semantic memory.

Studies examining the component analyses of verbal fluency have also provided evidence of the underlying brain regions responsible for clustering and
switching abilities. Specifically, while switching abilities may be primarily mediated by executive functioning and underlying frontostriatal regions, clustering may be more reliant on the integrity of the semantic store and temporal lobe functioning (e.g., Troyer et al., 1998b). In support of this notion, research has demonstrated activation in frontal regions during category fluency switching performance (Hirshorn & Thompson-Schill, 2006), and has found category fluency switching abilities to be particularly impaired relative to clustering in conditions affecting the integrity of frontostriatal brain systems (e.g., Huntington’s disease, Parkinson’s disease; Ho et al., 2002; Tröster et al., 1998), including HIV infection (Iudicello et al., 2007; Millikin et al., 2004; Woods et al., 2004). Given this evidence, along with results from this study suggesting that category fluency impairment observed in this older HIV+ cohort may be driven by impairments in switching, rather than clustering, it may suggest additional frontostriatal dysfunction, rather than an increased burden of age and HIV on temporal lobe structures, in older HIV infected individuals. This is also consistent with evidence of greater pathological and structural brain abnormalities within the frontostriatal regions in older HIV infected individuals (e.g., Ernst & Chang, 2004; Jernigan et al., 2005; Wiley et al., 1998).

One of the most profound complexities inherent in examining the neural and neuropsychological sequelae in older HIV infected individuals is delineating the adverse effects that may be attributed to aging relative to those that may be associated with HIV infection. The interplay between the normal aging process and HIV disease progression on the CNS remains poorly understood, and while it is possible that HIV infection may exacerbate the aging process, it is also likely that aging may accelerate
HIV disease progression. In general, research has demonstrated that older age may be associated with more rapid immunological decline, a shorter mean time from HIV diagnosis to death, a longer overall duration of disease, greater exposure to antiretroviral medications, and poorer responses to antiretroviral therapies (e.g., Adler et al., 1997; Cherner et al., 2004; Goetz, Boscardin, Wiley, & Alkasspooles, 2001; Grabar et al., 2004; Operkalski et al., 1995; Phillips et al., 1991; Valcour et al., 2004). However, the cognitive consequences of this interplay between HIV infection and aging remain unclear.

Results of this study suggest that switching impairment with in the older HIV infected sample could not be attributed to traditional markers of disease severity (i.e., current and nadir CD4 lymphocyte counts, plasma and CSF viral loads), or treatment characteristics (i.e., proportion on antiretroviral medications). For example, although 71% ($N = 44$) of the older HIV infected sample met criteria for AIDS, and roughly 78% ($N = 46$) of the older HIV infected group was on antiretroviral medications at the time of testing, there was no observed effect of AIDS or medication on switching performance. In addition, no associations were found between switching impairment and duration of HIV infection, current and nadir CD4 count, and plasma and CSF viral loads. While this was somewhat surprising given the literature supporting an association between markers of HIV disease progression (e.g., CSF viral load) and cognitive impairment (Ellis et al, 2002) as well as between AIDS status and verbal fluency switching in particular (e.g., Millikin et al., 2004), it is nonetheless consistent with our previous clustering and switching study in HIV infection (Iudicello et al., 2008), where we also did not find associations between switching impairment and
HIV disease characteristics (i.e., use of cART, AIDS status, plasma HIV viral load, current or nadir CD4 count, or duration of infection).

One explanation for these null findings, in addition to the absence of an HIV effect on switching in the older adults, may be that it the adverse effects of HIV disease progression may not be present in light of immune reconstitution, as the older HIV-infected sample in this study was relatively healthy, with only 16% considered immunosuppressed (i.e., CD4 lymphocyte counts < 200/µl). However, when only examining those older HIV infected adults who were immunosuppressed (n = 9) relative to their older HIV seronegative counterparts, there still was effect of HIV infection on switching performance. Alternatively, it may be that traditional markers of HIV disease severity (e.g., plasma viral load) may not be as good of an indicator of CNS damage and disease progression in the era of cART (e.g., Reger et al., 2005). As mentioned above, despite the introduction of cART, which has reduced morbidity and mortality in HIV through reducing plasma viral loads and restoring immune functioning, the prevalence of HIV associated cognitive disorders continues to be a problem. While some existing biomarkers (e.g., CSF viral load) appear to have some utility at detecting disease progression and subsequent cognitive impairment in some HIV infected individuals (e.g., Ellis et al., 2002), other HIV disease markers (e.g., plasma viral load, CD4 lymphocyte count) may not be as sensitive (e.g., Cysique et al., 2006; Ellis et al., 1997; Reger et al., 2002; cf. Stankoff et al., 1999). Thus, there is a need to identify alternate biomarkers of HIV associated neural injury (e.g., neuroaxonal injury, astrocytosis, and macrophage activation) that may be more informative with regard to the underlying mechanisms of HIV-associated brain
dysfunction and the subsequent cognitive impairment found in HIV infected individuals.

Recently, studies have begun to address the possible association between neurocognitive deficits in HIV infection and biomarkers of HIV-associated neural injury (e.g., Pemberton & Brew, 2001; Woods et al., 2006b; Woods et al., 2009b). For example, Woods et al., (2009b) found an association between poorer performance on the action (i.e., verb) fluency paradigms and higher levels of CSF s100ß (i.e., indicative of astrocyte activation), independent of traditional HIV disease markers (i.e., current immune compromise), antiretroviral therapy, and cognitive impairment (i.e., HIV Dementia Scale). Moreover, increased t-tau and p-tau concentrations (Brew, et al., 2005), higher levels of s100ß (e.g., Pemberton & Brew, 2001) and decreased CSF amyloid beta (Brew et al., 2005) have been found in HIV infected individuals with HAD. Of particular relevance to this current study, Woods et al., (2010) also found a marginal association between animal fluency performance and total Tau (i.e., a marker of neuroaxonal damage), such that poorer animal fluency output was associated with higher levels of Tau, indicating greater neural damage. Taken together, this evidence suggests that biomarkers of HIV disease may be more sensitive markers of HIV associated CNS disturbance, and may be better at detecting the presence and severity of HIV associated neural damage and cognitive impairment relative to traditional HIV disease indicators (e.g., CD4 count).

Lastly, with regard to HIV disease characteristics, while roughly 77% of the older, HIV infected group was on antiretroviral medications at the time of testing, there was no observed effect of medication status on switching performance. While
research has demonstrated that combination antiretroviral therapy (cART) has
decreased the incidence and prevalence of HAD (e.g., Heaton et al., 2009; Sacktor et
al., 2001), the prevalence of HIV-associated neurocognitive disorders (HAND)
continues to be a problem. While the underlying mechanisms remain unclear, it may
be a function of the antiretroviral regimen and the effectiveness with which it
significantly reduces viral loads. For example, despite the general effectiveness of
cART, some individuals continue to show incomplete viral suppression. Consistent
with this, while a majority of the older HIV cohort who were on cART had
undetectable viral loads (86%; n = 37), 14% (n = 6) showed persistent viral loads
despite cART. Despite the small sample of individuals with detectable plasma loads,
they still demonstrated impaired performance on the switching task relative to those
with undetectable viral loads ($p = 0.03$, Cohen's $d = 0.71$). While extremely
preliminary, and limited by the absence of data regarding adherence and medication
characteristics (e.g. CNS penetration ability), it highlights the need for future research
into the effectiveness of cART regimens and its association with cognitive
functioning. There is evidence from both cross-sectional (e.g., Ferrando et al., 1998),
and longitudinal research studies (e.g., Robertson et al., 2004), to suggest that
antiretroviral therapy may improve aspects of neuropsychological functioning,
especially with highly-CNS penetrating regimens (e.g., Letendre et al., 2004). Thus,
given the high prevalence of cognitive impairment in older HIV infected individuals,
further research on the effects of highly penetrating antiretroviral drug regimens and
their relationship to cognitive functioning are needed, as it may ultimately aid in the
amelioration of the cognitive decline that may be observed in older HIV infected adults.

Another inherent complexity in examining the mechanisms responsible for cognitive impairment in older HIV infected individuals is the number of concomitant neurodegenerative, medical, psychiatric and substance use disorders that are common in older HIV infected individuals and have been independently associated as risk factors for cognitive decline. For example, while controversial, some studies have suggested that Alzheimer’s disease (AD)-like changes in the CNS may occur in older HIV infected adults, which may contribute to the observed cognitive deficits found in this cohort. For example, research has demonstrated an increase in amyloid beta deposition (e.g., Achim et al., 2009; Brew & Pemberton, 2004; Green et al., 2005) and increased t-tau and p-tau concentrations similar to AD in demented HIV infected older adults. However, preliminary research examining the cognitive impairment profile in older HIV infected adults found that, while age and HIV infection may independently contribute to neuropsychological impairment (e.g., learning and memory and executive functions) in their older HIV cohort, that the pattern of impairment did not appear similar to the pattern of cognitive decline observed in early stage Alzheimer's patients (Scott et al., 2010).

Similarly, the pattern of category fluency impairment observed in this Older HIV infected cohort (i.e., impaired switching in light of intact clustering) argues against the controversial hypothesis that the pattern of cognitive impairment observed in older HIV may resemble that found in conditions typically associated with a more "cortical" neuropathogenesis (e.g., Alzheimer's disease). While HIV-associated
cognitive impairment has typically been linked to a primarily subcortical neuropathogenesis (e.g., Kieburtz et al., 1996; Ragin et al., 2005), recent evidence in the cART era has also demonstrated an impact of HIV infection on cortical brain regions as well (e.g., Everall et al., 1999; Moore et al., 2006), which may be particularly evident in advanced disease (e.g., Kruman, Nath, & Mattson, 1998). Unfortunately, this current study does not allow for direct inferences with regard to the potential associations between AD-like pathological features and category fluency impairment in older HIV infected individuals. However, research on clustering and switching abilities in AD has demonstrated that both clustering and switching are impaired in AD (e.g., Troyer, et al., 1998b) which is consistent with the neuropathological changes associated with AD in both temporal and frontal lobe regions (e.g., Davies, Mann, Sumpter, & Yates, 1987). As mentioned above, this pattern of clustering and switching deficits was not observed in this older HIV infected cohort. Rather, while evidence for additive effects were found for switching, no decline in clustering was demonstrated in the older HIV infected adults relative to the other groups. While inconsistent with the clustering and switching patterns seen in AD, the pattern of clustering and switching deficits observed in this older HIV infected sample more closely resembles that seen in conditions with compromised frontal systems functioning (e.g., frontal lobe lesions, Parkinson’s disease; Troyer, et al., 1998; Troyer et al., 1998). Regardless, despite evidence from this study that may argue specifically against an AD-like cognitive profile in this older HIV infected cohort, the issue of possible coexisting neurodegenerative disorders remains a significant concern, and warrants further prospective research.
It is also unlikely that the switching impairment found in the Older HIV infected group could be better explained by potentially confounding vascular conditions which are commonly observed in older HIV infected populations (e.g., Kilbourne et al., 2001), and have been established as independent risk factors for cognitive decline in studies of normal aging (e.g., Harrington et al., 2000). Broad markers of cardiovascular diseases (which may be used to draw references with regard to the presence of cerebrovascular disease) such as those examined in this study (i.e., hypertension, diabetes mellitus, and hypercholesterolemia) are prevalent in older adults with HIV infection, and have been commonly associated with cognitive impairment in the aging literature (e.g., Harrington et al., 2000; Manschot et al., 2006). Moreover, preliminary studies examining the effects of vascular risk factors on cognition in older HIV infected adults has revealed cognitive deficits, although generally confined to the processing speed domain (Becker et al., 2009; Foley et al., 2010), which is consistent with models of cognitive decline in the aging literature (e.g., Salthouse 1993). However, within the older HIV infected cohort in this study, no significant associations were found between the three aforementioned vascular risk factors and switching impairment. While it is possible that the small proportions of individuals within the older HIV+ group who had hypertension (26%; n = 16), diabetes (22%; n = 11), or hypercholesterolemia (19%; n = 10), may have made it difficult to detect potential adverse effects of vascular risk factors on cognition in this cohort, these null findings are nonetheless consistent with the only above mentioned study that included a verbal fluency domain (i.e., FAS and animals; Foley et al., 2010) and did not find differences in verbal fluency performance between older HIV infected
individuals with and without vascular risk factors. However, research should continue to investigate the possible cognitive complications that may arise from vascular risk factors in older HIV infected individuals, as the risk for vascular cognitive impairment may become more apparent with age and with advancing and/or untreated vascular symptoms (e.g., Foley et al., 2010), and may have important implications for everyday functioning.

Within the older HIV+ group, switching impairment also did not appear to be related to HCV/HIV co-infection. While 25% (n = 14) of the individuals within the older HIV infected group were co-infected with HCV, they showed comparable performance to those with HIV infection alone. Research has demonstrated adverse cognitive effects of HCV infection alone (e.g., Perry et al., 2008; Hilsabeck et al., 2003) as well as in combination with HIV infection (e.g., Cherner et al., 2005; Martin et al., 2004), which may reflect damage to neural mechanisms sensitive to both HIV and HCV infection (i.e., frontostriatal circuitry). However, results from this study did not find greater switching in the co-infected individuals relative to those with HIV infection alone in this older HIV infected cohort, which is consistent with research demonstrating no additional burden of HCV disease on cognitive functioning in HIV infection (e.g., von Giesen et al., 2004) at least in the early stages of HCV disease. While speculative given that HCV disease characteristics were not available for the present study, it may be that the HCV/HIV infected individuals in this study may be in the earlier stages of disease (similar to von Giesen et al., 2004), or may not have a high degree of liver fibrosis, which has been associated with HCV-associated cognitive dysfunction (e.g., Perry et al., 2005). In addition, the small sample sizes in
the older adults also may have made it difficult to detect subtle adverse effects of HCV infection on cognition in older HIV infected adults. Regardless, given evidence to suggest that HCV/HIV co-infection may confer additional risk for neurocognitive impairment (e.g., Cherner et al., 2004), and that the presence of HCV infection may accelerate the course of HIV infection leading to potentially greater CNS damage, research should further examine the mechanisms underlying HCV/HIV co-infection and their relationship to age and neuropsychological functioning, in order to aid in the effective management and treatment of the cognitive consequences of HIV/HCV co-infection in older individuals.

While the older HIV infected group endorsed significantly more affective symptoms overall relative to both the older and younger HIV seronegative groups (but not relative to the younger HIV+ group), it does not appear that current affective distress is related to the pattern of switching impairment across the groups over and beyond that which can be attributed to effects of age and HIV infection. Although current mood status was a significant predictor of switching, the effects of HIV infection and aging still remained when it was included in the statistical model predicting fluency performance. While most of the prior research on mood factors in HIV infection (e.g., depression) has suggested that there may not be an additional cognitive burden due to mood factors in HIV infection (e.g., Cysique et al., 2007; Grant et al., 1993; Rourke et al., 1999), some studies have found an association between depression and cognitive declines in normal aging populations (e.g., slowed information processing speed; Butters et al., 2004). Given that the older HIV infected group did not differ from their younger HIV infected counterparts in terms of current
mood status, but endorsed a greater number of mood symptoms relative to the older, seronegative group, it may be thought that mood symptoms played a slight role in the relatively greater switching impairment observed older HIV infected sample. However, no significant associations were seen between current affective distress and poorer switching performance when examined only in this cohort. Nonetheless, future research should examine the effects of mood symptoms in older HIV infected individuals, as depression, or mood symptoms in general, may be more prevalent in older HIV infected individuals, and if present, cognitive declines that may be attributable to depression may be alleviated with successful treatment, which may in turn lead to improvements in overall quality of life.

Several inherent limitations within this study are worth noting. First, this study tested an additivity model regarding the effects of aging and HIV infection, thus inferences regarding potential interactive or synergistic effects of aging and HIV infection may not be gleaned from these results. In other words, these results demonstrate that the dual presence of aging and HIV infection may have a greater impact on cognitive functioning relative to either aging or HIV infection alone, which in turn may have more adverse effects relative to the absence of both risk factors. However, this model is unequipped to provide information regarding potential differential effects that HIV infection may have on the CNS in the older adults relative to younger adults or whether the effects of normal aging may be accelerated in the setting of HIV infection. Such information provides valuable insight into the mechanisms underlying the interplay between HIV and aging and should be further examined, alongside research exploring the additive effects of HIV and aging, in order
to gain a better understanding of the neural and cognitive sequelae observed in older HIV infected individuals.

In addition, despite results indicating an overall additive effect of HIV and aging on switching performance, the HIV effect was surprisingly not observed between the older groups. It is unlikely that the lack of association between HIV infection and switching performance in the older cohorts reflects demographic factors or rates of comorbid medical conditions (i.e. hypertension, hypercholesterolemia, diabetes mellitus), as these characteristics did not differ between the groups. However, there are a few explanations that may explain these null findings. First, while comparable at the group level, there were high rates of hepatitis C virus in both the Older HIV- (38%; \(n=18\)) and Older HIV+ (25%; \(n=14\)). As mentioned above, Hepatitis C virus has been associated with cognitive decline, both independently (e.g., Perry, Hilsabeck & Hassanein, 2008), and in the setting of HIV infection (Hilsabeck et al., 2005; Martin et al., 2004). While speculative, it is possible that the absence of an HIV effect on switching between the two older groups is reflective of differences in HCV disease characteristics, such as a greater liver fibrosis stage, which has been associated with poorer cognitive test performance in HCV infection (Hilsabeck, Perry, & Hassanein, 2002). However, this study did not have the resources to explore this hypothesis.

Another hypothesis is that the absence of an HIV effect on switching within the older samples may be attributed the potentially adverse neuropsychological sequelae of substance use disorders, given the prevalence of co-morbid substance use in HIV infected individuals and the well documented independent deleterious effects
of substance use (e.g., methamphetamine) on the CNS within HIV infected individuals (e.g., Chang et al., 2007; Carey et al., 2006). While one study showed post hoc that the removal of individuals with substance use from their sample did not affect neuropsychological impairment rates in older HIV infected adults (Cherner et al., 2004), a greater number of these individuals reported abuse rather than dependence, thus the presence of more severe substance use (i.e., dependence) may confer additional risk for neuropsychological impairment in older HIV infected cohorts. Unfortunately, due to the inclusion of participants from different protocols, a consistent measure of lifetime substance (i.e., alcohol and illicit drug) use was not available for this study. Future research should carefully examine the potential neuropsychological sequelae of substance use disorders in older HIV infected individuals in order to more accurately differentiate the potential etiologies of cognitive impairment in older HIV infected individuals.

A more likely explanation for the null HIV effect on switching may be that the prevalence of severity of cognitive impairment in HIV infected individuals varies widely. Approximately 43% \((N = 27)\) of this Older HIV infected cohort was neuropsychologically impaired (i.e., HAND; for classification systems, see above), whereas 57% were classified as neuropsychologically unimpaired. Thus, the substantial proportion of individuals who demonstrate better neurocognitive abilities may be attenuating an HIV effect within the older groups. Indeed, Older HIV infected individuals who were neuropsychologically impaired showed significantly worse performance relative to the Older HIV- group \( (p = 0.024, \text{Cohen's } d = 0.56)\), suggesting a subset of older HIV+ individuals with HAND that in fact do demonstrate
significantly poorer switching abilities relative to older HIV- individuals. These results could not be better explained by demographic characteristics (e.g., age, education, ethnicity, and sex) or HCV status.

Finally, while the mean age of the older HIV+ cohort in this study (mean = 58.2, standard deviation = 6.2) was relatively young relative to traditional cognitive aging studies, it is consistent with, and, of note, a few years older than the typical average age of older HIV infected cohorts in the current HIV/aging literature. It is possible that more prominent age effects may be observed in samples with substantial proportions of individuals who are older than 60 years of age. In addition, individuals within the older HIV infected group were generally healthy in terms of HIV disease characteristics (only 30% had detectable viral loads, mean current CD4 count = 435 cells/µl), were predominantly Caucasian (approximately 75%), and mostly male (approximately 83%), which may limit the generalizability of these findings to HIV infected older individuals with more advanced disease or differing demographics.

Lastly, an important issue to consider in HIV and aging research that may confer additional sample issues is the notion of survival bias. That is, older individuals with HIV infection may represent a unique sample of the HIV population, as they tend to have longer durations of HIV disease, and thus have lived longer and have been exposed to the effects of HIV disease on the CNS for longer periods of time. Thus, some of the observed cognitive impairment observed in this older HIV infected cohort may be attenuated by an attrition of those who may have survived for long periods of time without substantial HIV-associated CNS damage. Future research is needed in order to explore the relationship between disease duration and neuropsychological
impairment in older HIV infected adults in order to examine potential protective factors against decline, which would aid in the rehabilitation of HIV associated neurocognitive disorders.

Of important clinical significance, results of this study suggested that switching impairment in older HIV infected adults was a significant predictor of self-reported declines in instrumental activities of daily living (IADLs) in the older HIV infected group, even when accounting for potentially confounding variables that differed between those considered to be dependent in activities of daily living relative to their independent counterparts, (i.e., education, duration of HIV infection, and affective distress). It is unlikely that other demographic (i.e., age, ethnicity, gender), medical (i.e., Hepatitis C, vascular risk factors), or HIV disease (i.e., Nadir CD4 Count, plasma and CSF viral load) characteristics influenced everyday functioning within this older HIV infected cohort, as no significant differences were found between the IADL Independent and Dependent Groups on these variables. Of clinical significance, switching showed good specificity (i.e., 86%) to IADL dependence in the older HIV infected cohort, with a 73% hit rate in discriminating between the IADL dependent and independent group. Individuals who scored below the cutoff (i.e., 7 switches) were over seven times more likely to be classified as IADL dependent relative to those with scores above the cutoff (odds ratio = 7.6).

Collectively, these data are consistent with prior research highlighting the important relationship between neuropsychological impairment, and specifically, verbal fluency, and declines in everyday functioning in both HIV infection (e.g., Heaton et al., 2004; Woods et al., 2008) and in normal aging (e.g., Cahn-Weiner,
Boyle, & Malloy, 2002). Moreover, of the seven cognitive domains included in Heaton et al. (2004)’s study on functional dependence in HIV infection, executive functioning and learning were among the best predictors of failures on performance based standardized tests of IADL failures. Cahn-Weiner et al. (2002) also found that executive dysfunction in older individuals may be the strongest predictor of cognitive decline in the elderly. Taken collectively, and alongside the above-mentioned associations between switching performance and learning and executive functioning abilities in the older HIV infected individuals, these data provide support for the ecological validity and enhances the clinical utility of category fluency switching as a predictor of IADL dependence in older HIV infected individuals and as a potential useful diagnostic tool in determining whether older individuals with HIV infection may be particularly vulnerable to declines in everyday functioning.

Not surprisingly, greater overall affective distress (i.e., POMS Total Mood Disturbance) was also a significant predictor of self-reported declines in everyday functioning in the older HIV infected cohort, which is consistent with research demonstrating that mood factors (e.g., depression) are significant predictors of decline in everyday functioning abilities, as measured by both self-report measures (e.g., Woods et al., 2004) and laboratory based functional tests (Heaton et al., 2004) in HIV infection. Moreover, Heaton et al. (2004) found that depression, as measured by the BDI, was predictive of declines everyday functioning independent of neuropsychological impairment. Thus, while some HIV infected individuals may have the cognitive abilities and thus the potential to function independently in everyday life, their mood status may negatively interfere, causing both subjective and objective
declines in everyday functioning. Of note, closer examination of the specific subscales within the POMS self-report measure revealed that of the six subscales (i.e., tension/anxiety, depression/dejection, anger/hostility, fatigue/inertia, and confusion/bewilderment), the confusion/bewilderment subscale was the only significant independent predictor of IADL dependence ($p = 0.010$). This suggests that while affective distress within this Older HIV infected cohort may undoubtedly lead to consequences on everyday functioning, that the cognitive sequelae that is experienced by older HIV infected individuals may prove to be an even greater risk factor than mood symptoms for declines in everyday functioning. Of clinical relevance, to the extent that depression may be treatable in older HIV infected individuals, this evidence provides support for the benefits of early detection and treatment of mood symptoms in older HIV infected adults, which may aid in the remediation of the functional declines that may coincide with HIV and aging.

In conclusion, this present study provides preliminary evidence for additive adverse effects of HIV infection and normal aging on the executive components of semantic verbal fluency, which may reflect concomitant deleterious effects of age and HIV infection on frontostriatal circuits. In order to more clearly understand the neural mechanisms underlying cognitive impairment in older HIV infected adults (and across the age spectrum), future research should focus on the identification of more sensitive biomarkers of HIV-associated neural injury and their associations with cognitive decline in older HIV infected cohorts. The vast utility of biomarker research in HIV disease would be even greater if also complimented by imaging studies, which would aid in the specification of brain regions that may be particularly vulnerable to HIV
neuronal injury (e.g. astrocytosis). Such research is critical, and may have important clinical implications with regard to the diagnosis of neurocognitive disorders in older HIV infected adults, to the selection of the most appropriate and effective treatment for HIV associated CNS damage, and to the improvement in overall quality of life, in individuals aging with HIV.
VI. References


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